Radical Synthesis of Highly Substituted Boc-Protected 4-Aminomethyl-Pyrroles

Introduction

Pyrroles represent indispensable structural motifs of biologically active alkaloids, pharmaceutical products, or even materials such as conducting polymers.[142] For instance, lipitor, a pyrrole based hypochloremic agent, was for many years the largest selling drug, with annual sales in excess of 10 billion U.S. Dollars.[143] 2,4-Disubstituted pyrroles are especially interesting since they are useful intermediates for the synthesis of more highly substituted derivatives and are present in a few pharmacologically significant products.[144] Three examples of 2,4-disubstituted pyrrole natural products are displayed in Figure 5.1: Hymenidin is an antagonist of serotonergic receptors; pyrrolostatin is a potent inhibitor of lipid peroxidation, and heronapyrroles A and B display antibiotic activity against Gram-positive bacteria such as Staphylococcus aureus and Bacillus subtilis.

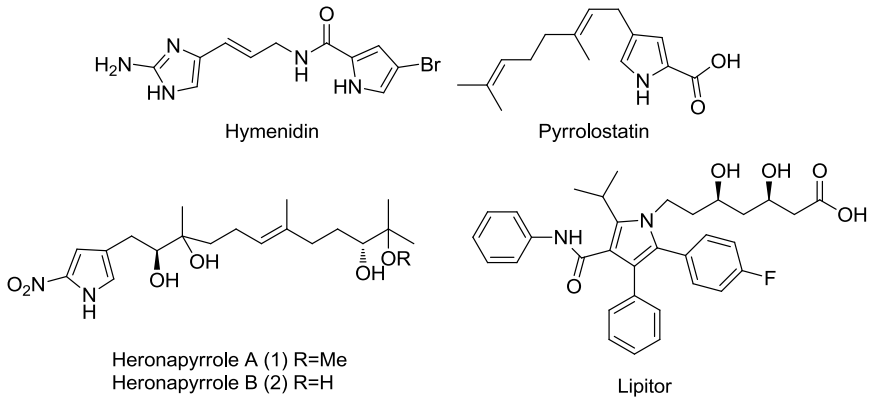


Figure 5.1 Structures of biologically active pyrroles

[142] (a) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.; *Chem. Rev.*, 2008, **108**, 264. (b) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. *Nat. Prod. Rep.*, 2006, **23**, 517. (c) Gale, P. A. *Acc. Chem. Res.* 2006, **39**, 465. (d) Baraldi, P. G.; Nunez, M. C.; Tabrizi, M. A.; De Clercq, E.; Balzarini, J.; Bermejo, J.; Esterez, F.; Romagnodi, R. *J. Med. Chem.*, 2004, **47**, 2877. (e) Srivastava, S. K.; Shefali Miller, C. N.; Aceto, M. D.; Traynor, J. R.; Lewis, J. W.; Husbands, S. M.; *J. Med. Chem.*, 2004, **47**, 6645.

[143] Thompson, R. B. *FASEB J.* **2001**, *15*, 1671.

[144] (a) Bergauer, M.; Hubner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1937. (b) Kobayashi, J.; Ohizumi, Y.; Nakamura, H.; Hirata, Y. *Experientia* **1986**, *42*, 1176. (c) Han, S.; Siegel, D. S.; Morrison, K. C.; Hergenrother, P. J.; Movassaghi, M. *J. Org. Chem.* **2013**, *78*, 11970. (d) Kato, S.; Shindo, K.; Kawai, H.; Odagawa, A.; Matsuoka, M.; Mochizuki, J. *J. Antibiot.* **1993**, *46*, 892. (e) Raju, R.; Piggott, A. M.; Barrientos Diaz, L. X.; Khalil, Z.; Capon, R. J. *Org. Lett.* **2010**, *12*, 5158.

There are numerous synthetic methods for the construction of pyrrole structures. In this chapter, therefore the classic named reactions and current methods for the preparation of pyrroles will be briefly discussed. However, the limitations of most known approaches to access 2,4-disubstituted and polysubstituted pyrroles bearing a protected aminomethyl group encouraged us to apply our typical radical addition process for the construction of such pyrroles. Thus, the scope and advantages of our newly designed protocol for the preparation of 2-disubstituted, 2,3-trisubstituted and polycyclic, boc-protected 4-aminomethyl-pyrroles will also be then described in this chapter.

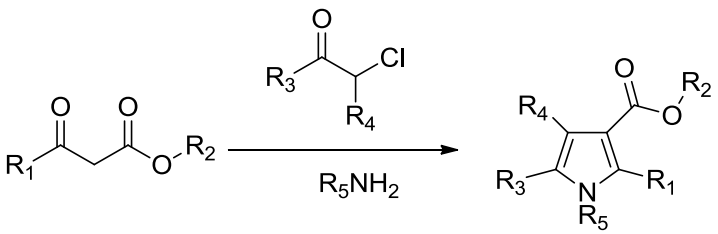
Ⅰ. Synthesis of pyrroles

1. Named reactions for pyrrole synthesis

There is a plethora of methods to access pyrroles, especially the classical named reaction such as the Hantzsch synthesis, Paal–Knorr synthesis or Barton-Zard reaction which open up numerous opportunities for the synthesis of pyrroles.

1.1. The Hantzsch Pyrrole Synthesis

In 1890, Hantzsch reported the preparation of pyrroles via the condensation of *α*-halo-ketones, *β*-ketoesters and ammonia or amines, which is generally referred to as the Hantzsch pyrrole synthesis or Hantzsch synthesis (Scheme 5.1).[145]

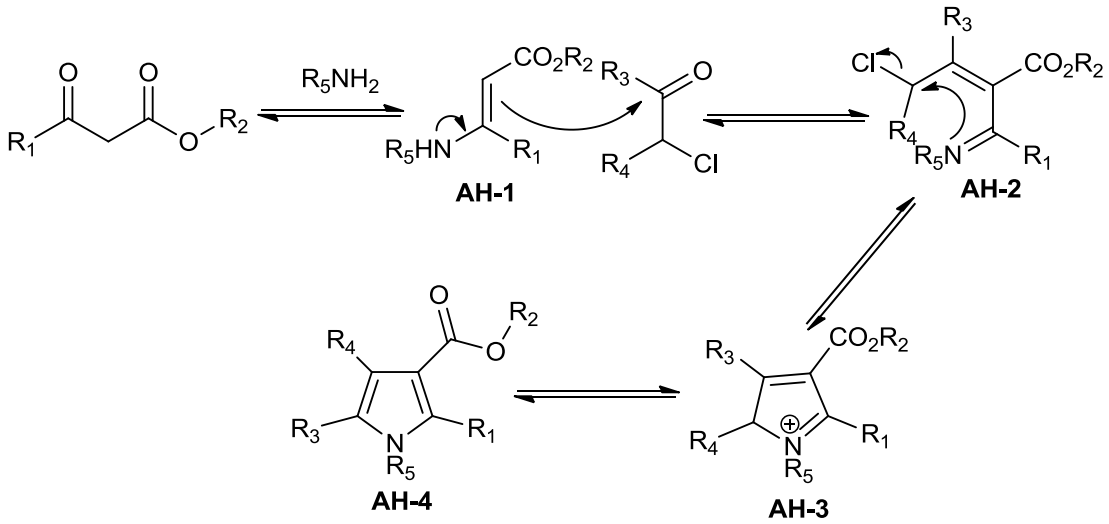


Scheme 5.1 Hantzsch pyrrole synthesis

The mechanism is outlined in Scheme 5.2. Condensation of ammonia or primary amine with *β*-ketoesters gives enamine **AH-1,** which then attacks the carbonyl carbon of the *α*-haloketone to furnish intermediate **AH-2**. This is quickly converted to 5-membered ring **AH-3** *via* an intramolecular nucleophilic attack. Finally, the aromatization of **AH-3** affords the corresponding pyrrole **AH-4**. Since this reaction consists of three components, a wide scope of functional groups could in principle be incorporated by replacing the substituents on the different components to give

[145] (a) Hantzsch, A. *Ber*. **1890**, *23*, 1474. (b) Katritzky, A. R.; Ostercamp, D. L.; Yousaf, T. I. *Tetrahedron* **1987**, *43*, 5171. (c) Kirschke, K.; Costisella, B.; Ramm, M.; Schulz, B. *J. Prakt. Chem*. **1990**, *332*, 143. (d) Kameswaran, V.; Jiang, B. *Synthesis* **1997**, 530.

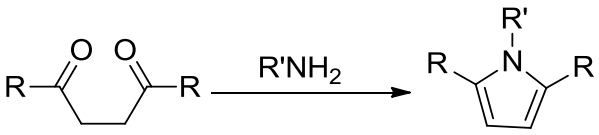
numerous pyrrole derivatives.[146] The Hantzsch synthesis can be considered as the most appropriate approach for accessing highly substituted pyrroles. Furthermore, this reaction has been extended to the preparation of indoles and carbazoles.



Scheme 5.2 Mechanism of the Hantzsch pyrrole synthesis

1.2. The Paal–Knorr pyrrole synthesis

Knorr initially described this synthesis in 1884 and later the condensation between 1,4-dicarbonyls and primary amines (or ammonia) giving pyrroles was defined as the Paal-Knorr Pyrrole Synthesis (Scheme 5.3).[147]

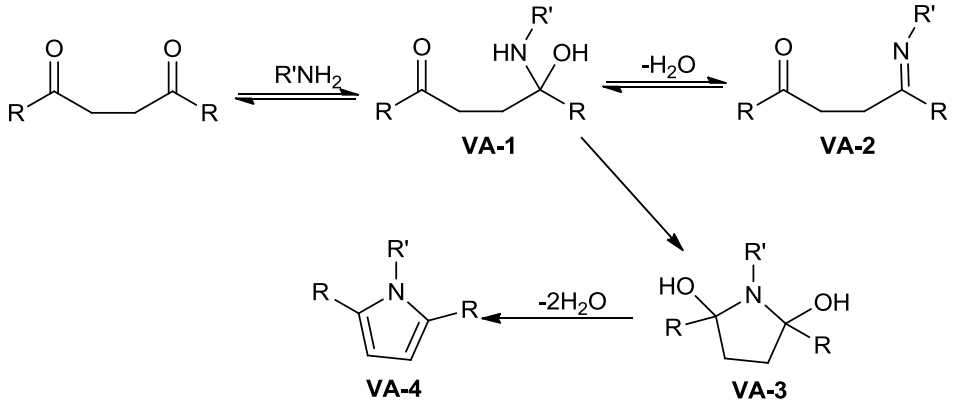


Scheme 5.3 The Paal–Knorr pyrrole synthesis

[146] (a) Trautwein, A. W.; Süβmuth, R. D.; Jung, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2381. (b) Ferreira, V. F.; De Souza, M. C. B. V.; Cunha, A. C.; Pereira, L. O. R.; Ferreira, M. L. G. *Org. Prep. Proced. Int.* **2001**, *33*, 411.

[147] (a) Paal, C. *Ber.* **1885**, *18*, 367. (b) Chiu, P. K.; Sammes, M. P. *Tetrahedron* **1988**, *44*, 3531. (c) Gribble, G. W. *Knorr and Paal–Knorr Pyrrole Syntheses*. In *Name Reactions in Heterocyclic Chemistry*; Li, J. J., Corey, E. J., Eds, Wiley: Hoboken, NJ, **2005**, 77.

Amarnath and co-workers investigated the mechanism of this process (Scheme 5.4).[148] Their work suggested that hemiaminal **VA-1** is a crucial intermediate that is formed by the nucleophilic attack of the amine on the ketone under acidic conditions. The hemiaminal **VA-1** then undergoes an intramolecular nucleophilic attack to afford intermediate **VA-3** followed by the dehydration to furnish the corresponding pyrrole **VA-4**. All 1,4-dicarbonyls, *α*-amino ketones or *α*-amino-*β*-ketoesters can be converted into the corresponding pyrroles by modification of this method. The reaction requires mild acidic conditions and tolerates a wide range of functional groups. These advantages make the Paal–Knorr a powerful tool for pyrrole synthesis.[149]



Scheme 5.4 Mechanism of the Paal–Knorr pyrrole synthesis

1.3. The Barton-Zard reaction

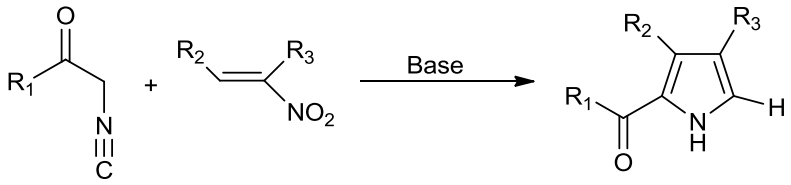
In 1986, Barton and Zard reported the formation of pyrroles *via* condensation of a substituted nitro-alkene with an isocyanoester in the presence of base. This is now called the Barton-Zard pyrrole synthesis (Scheme 5.5).[150] It is particularly adapted for the synthesis of pyrroles with various substituents at the 3,4 positions (R_2 and R_3) and the 2 position can be temporally blocked by a *t*-butyl carboxylate, a group that is

[148] Amarnath, V.; Anthony, D. C.; Amarnath, K.; Valentine, W. M.; Wetterau, L. A.; Graham, D. G. *J. Org. Chem.* **1991**, *56*, 6924.

[149] (a) Salamone, S. G.; Dudley, G. B. *Org. Lett.* **2005**, *7*, 4443. (b) Fu, L.; Gribble, G. W. *Tetrahedron Lett.* **2008**, *49*, 7352.

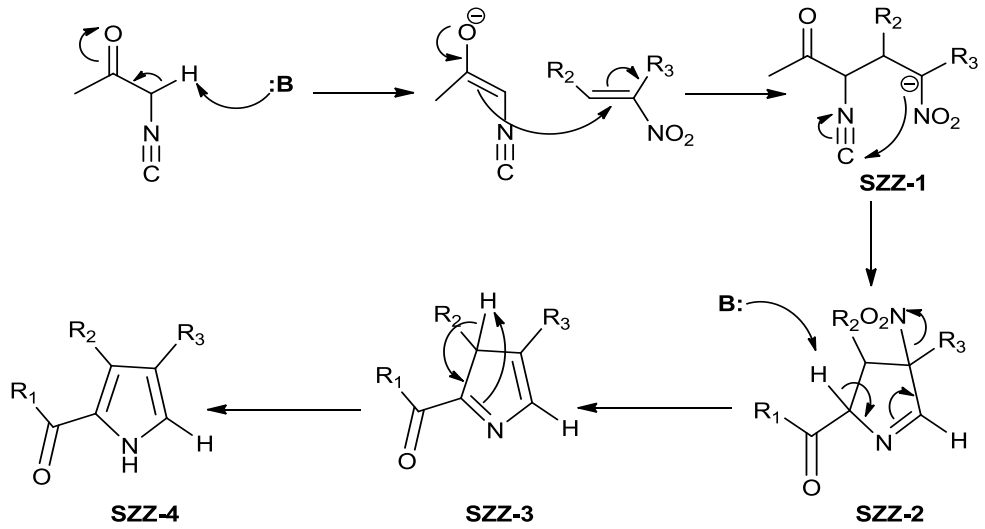
[150] (a) Barton, D. H. R.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1985**, 1098. (b) Barton, D. H. R.; Kervagoret, J.; Zard, S. Z. *Tetrahedron* **1990**, *46*, 7587.

difficult to introduce by other procedures.[151] The preparation of functional dyes, polypyrroles, and porphyrins fused with various aromatic rings or bicyclic frameworks have been achieved *via* this approach.[152]



Scheme 5.5 The Barton-Zard reaction

The mechanism is shown in Scheme 5.6. In the presence of base the deprotonated *α*-isocyanide undergoes Michael addition with the nitroalkene to form adduct **SZZ-1**. This is then converted into 5-member ring intermediate **SZZ-2** *via* an intramolecular nucleophilic attack. Finally, the base catalyzed elimination of a nitrite transforms **SZZ-2** into **SZZ-3** followed by aromatization to the corresponding pyrrole **SZZ-4**.



Scheme 5.6 Mechanism of the Barton-Zard reaction

[151] (a) Pelkey, E. T.; Chang, L.; Gribble, G. W. *Chem. Commun.* **1996**, 1909. (b) Ono, N.; Hironaga, H.; Ono, K.; Kaneko, S.; Murashima, T.; Ueda, T.; Tsukamura, C.; Ogawa, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 417.

[152] Lash, T. D.; Werner, T. M.; Thompson, M. L.; Manley, J. M. *J. Org. Chem.* **2001**, *66*, 3152.

2. Recent approaches to construct highly substituted pyrrole derivatives

The need for highly flexible and efficient syntheses of polysubstituted pyrroles has encouraged extensive studies to achieve this goal.[153] Therefore, besides classical named reactions, there has been a plethora of more recent methods for the synthesis of pyrroles, most of which are metal-based or 1,3-dipolar cycloaddition strategies.[154] In the following part, three illustrations of recent approaches to afford highly substituted pyrrole derivatives will be briefly discussed.

2.1. The Hantzsch pyrrole synthesis by using high-speed vibration milling technique

Recently, Menendez and co-workers reported a flexible one-pot process to access highly substituted pyrroles under solvent-free conditions.[155] As shown in Scheme 5.7, the system consisted of ketone **JCM-1**, a primary amine and a *β*-dicarbonyl compound. First, the mixture of ketone **JCM-1** and *N*-iodosuccinimide was heated in the presence of *p*-toluenesulfinic acid to generate intermediate **JCM-2** followed by addition of the primary amine, the *β*-dicarbonyl compound, and 5% cerium (IV) ammonium nitrate (CAN) as the catalyst and silver nitrate (1.0 eq. with

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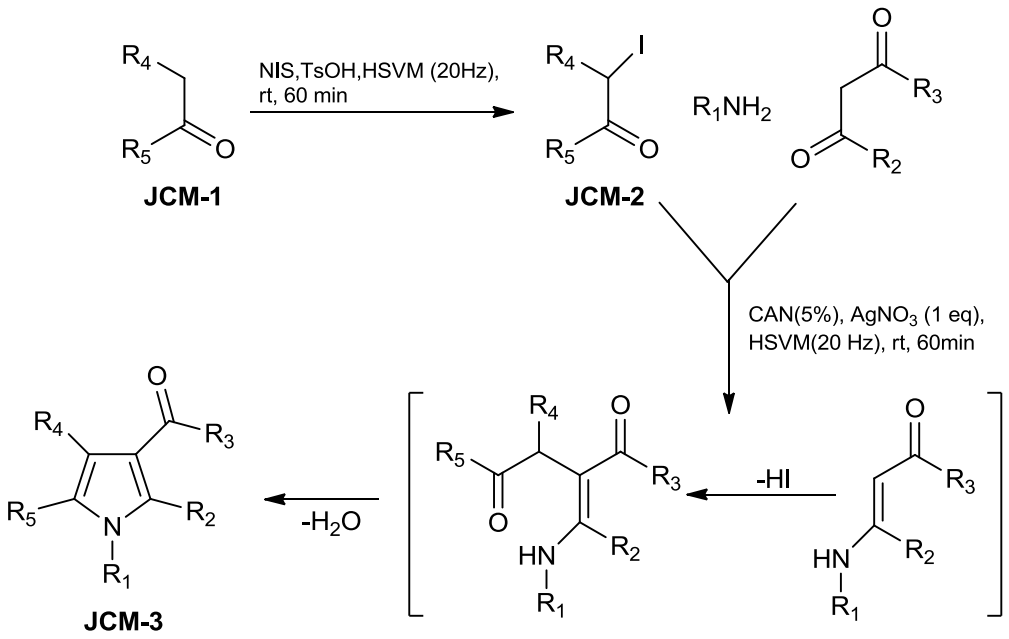
[153] (a) *Pyrroles, Part II;* Jones, R. A., Ed.; Wiley: New York, 1992. (b) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, U.K., 1996; Vol. 2, p 119ff.

[154] (a) Yan, R.; Kang, X.; Zhou, X.; Li, X.; Liu, X.; Xiang, L.; Li, Y.; Huang, G. *J. Org. Chem.* **2014**, *79*, 465. (b) Yeh, M.-C. P.; Lin, M.-N.; Hsu, C.-H.; Liang, C. J. *J. Org. Chem.* **2013**, *78*, 12381. (c) Zhou, Y.; Yan, X.; Chen, C.; Xi, C. *Organometallics* **2013**, *32*, 6182. (d) Shi, Y.; Gevorgyan, V. *Org. Lett.* **2013**, *15*, 5394. (e) Chaudhuri, R.; Uli Kazmaier, U. *Organometallics* **2013**, *32*, 5546. (f) Zhang, M.; Fang, X.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2013**, *135*, 11384. (g) Alford, J. S.; Spangler, J. E.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 11712. (h) Wang, X.; Xu, X.-P.; Wang, S.-Y.; Zhou, W.; Ji, S.-J. *Org. Lett.* **2013**, *15*, 4246. (i) Miura, T.; Hiraga, K.; Biyajima, T.; Nakamuro, T.; Murakami, M. *Org. Lett.* **2013**, *15*, 3298. (j) Hu, Y.; Wang, C.; Wang, D.; Wu, F.; Wan, B. *Org. Lett.* **2013**, *15*, 3146. (k) Feng, X.; Wang, Q.; Lin, W.; Dou, G.-L.; Huang, Z.-B.; Shi, D.-Q. *Org. Lett.* **2013**, *15*, 2542. (l) Gabriele, B.; Veltri, L.; Plastina, P.; Mancuso, R.; Vetere, M. V.; Maltese, V. *J. Org. Chem.* **2013**, *78*, 4919. (m) Chen, Z.; Lu, B.; Ding, Z.; Gao, K.; Yoshikai, N. *Org. Lett.* **2013**, *15*, 1966. (n) Parr, B. T.; Green, S. A.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 4716.

[155] Estevez, V.; Villacampa, M.; Menendez, J.C. *Chem. Commun.* **2013**, *49*, 59

respect to **JCM-1**) used to trap HI. Under these conditions, the desired pyrrole **JCM-3** could be formed after an additional one hour.

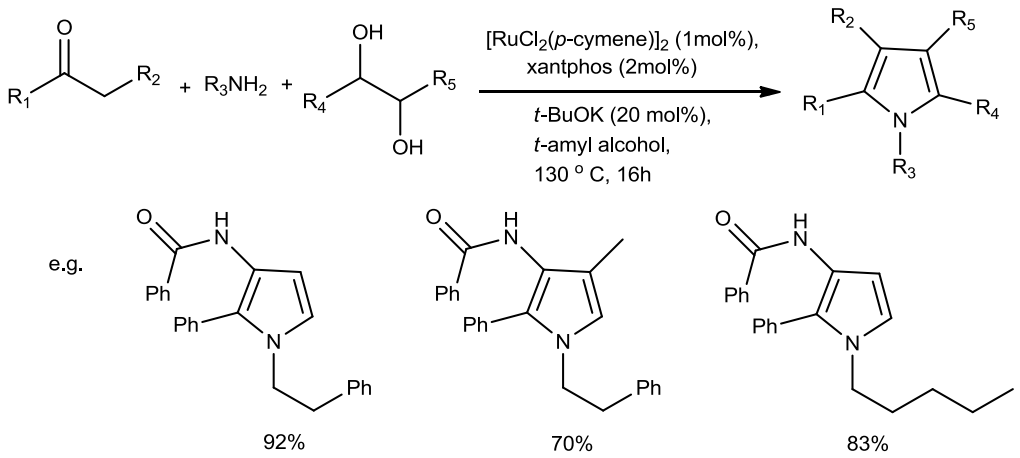


Scheme 5.7 Synthesis of pyrrole under solvent-free conditions

2.2. Pyrrole synthesis based on a ruthenium catalyzed reaction

A general and highly regioselective synthesis of pyrroles based on ruthenium catalysis was described by Beller and co-workers.[156] As shown in Scheme 5.8, in one pot process, various ketones, amines and vicinal diols were converted into the corresponding pyrrole in the presence of the commercially available ruthenium catalyst and a catalytic amount of base. All kinds of substituted pyrroles can be obtained by replacing the R groups in each component. In some cases, even an amide group could be attached to the pyrrole nucleus directly by this method.

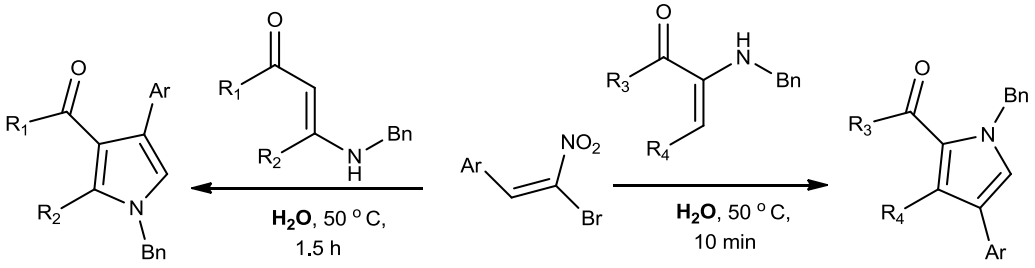
[156] Zhang, M., Fang, X., Neumann, H., Beller, M. *J. Am. Chem. Soc.* **2013**, *135*, 11384.



Scheme 5.8 Ruthenium catalyzed pyrrole synthesis

2.3. Synthesis of pyrroles by domino reaction in water

Most of the known methods for the synthesis of pyrroles require either harsh conditions or are based on metal catalyzed approaches. Recently, Rueping and co-workers applied a domino reaction for the synthesis of pyrroles.[157] As described in Scheme 5.9, and without involving in any metal catalyst, the reaction between (E)-*β*-bromonitrostyrenes and enaminones proceeded in water to furnish 2,3,4-trisubstituted pyrroles under mild conditions. The use of water offers environmental and industrial benefits.



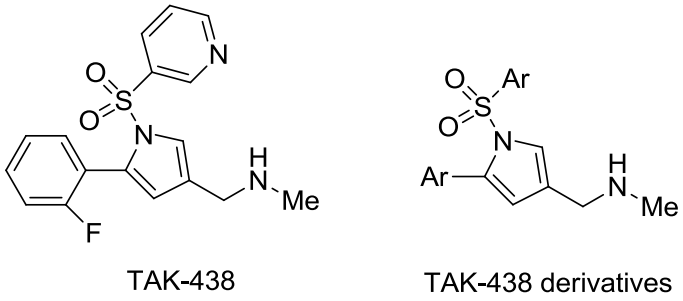
Scheme 5.9 Synthesis of pyrrole in water

[157] Rueping, M., Rarra, A. *Org. Lett.* **2010**, *12*, 5281

Π. Synthesis of TAK-438 and related aminomethyl substituted pyrroles

1. Synthesis of TAK-438

TAK-438 is an unusual pyrrole bearing a strong basic moiety that was discovered by Takeda (Scheme 5.10).[158] The Takeda chemists investigated the synthesis and structure-activity relationships of TAK-438 and its derivatives, which belonged to a new class of inhibitors called potassium-competitive acid blockers (P-CABs).[159] It has been found that the introduction of an aminomethyl group at the 4-position of the pyrrole ring improved its potential greatly as an unprecedented gastric antisecretory agent for the treatment of gastroesophageal reflux disease (GERD), peptic ulcer and other gastric acid-related diseases.[160] Recently, the Takeda Pharmaceutical Company Limited ("Takeda") has submitted a New Drug Application to the Ministry of Health, Labour and Welfare for TAK-438 (generic name: Vonoprazan Fumarate).



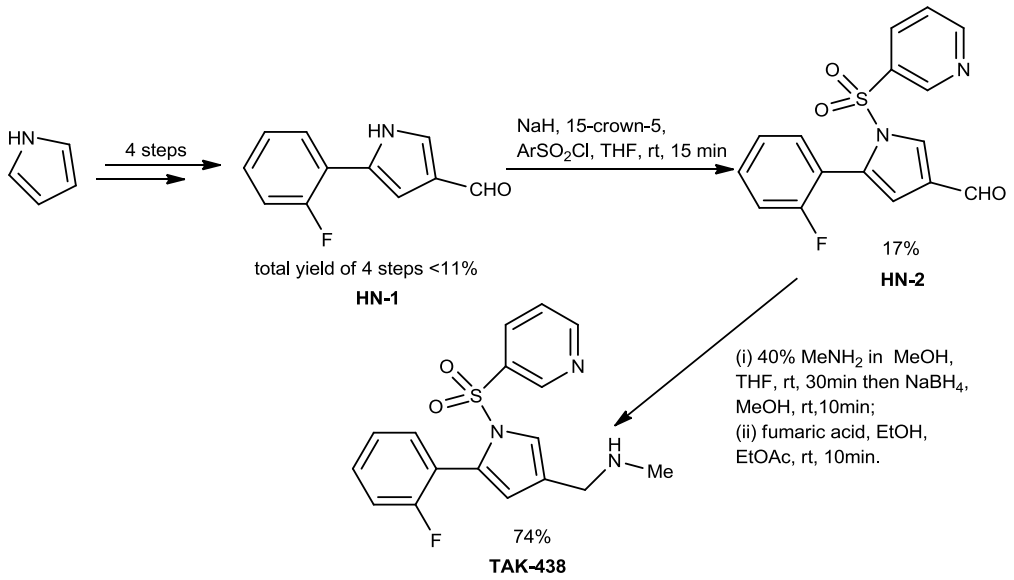
Scheme 5.10 TAK-438 and its derivatives

[158] Hori, Y.; Imanishi, A.; Matsukawa, J.; Tsukimi, Y.; Nishida, H.; Arikawa, Y.; Hirase, K.; Kajino, M.; Inatomi, N. *J. Pharmacol. Exp. Ther.* **2010**, *335*, 231.

[159] Hori, Y.; Matsukawa, J.; Takeuchi, T.; Nishida, H.; Kajino, M.; Inatomi, N. *J Pharmacol Exp Ther*. **2011**, *337*, 797.

[160] (a)Arikawa, Y.; Nishida, H.; Kurasawa, O.; Hasuoka, A.; Hirase, K.; Inatomi, N.; Hori, Y.; Matsukawa, J.; Imanishi, A.; Kondo, M.; Tarui, N.; Hamada, T.; Takagi, T.; Takeuchi, T.; Kajino, M. *J. Med. Chem.* **2012**, *55*, 4446. (b) Nishida, H.; Hasuoka, A.; Arikawa, Y.; Kurasawa, O.; Hirase, K.; Inatomi, N.; Hori, Y.; Sato, F.; Tarui, N.; Imanishi, A.; Kondo, M.; Takagi, T.; Kajino, M. *Bioorg Med Chem*, **2012,** *20*, 3925.

TAK-438 represents one of the unusual 2,4-disubstituted pyrroles which are tedious to obtain by current methods. The synthetic route to TAK-438 is outlined in Scheme 5.11. Pyrrole was converted into 5-(2-fluorophenyl)-1*H*-pyrrole-3-carb--aldehyde **HN-1** via four steps in very low total yield. In the presence of sodium hydride, sulfonylation of **HN-1** using 3-pyridine sulfonyl chloride gave **HN-2** in very low yield. Finally, the reductive amination of **HN-2** afforded TAK-438. This route is quite inefficient and room for considerable improvement exists.



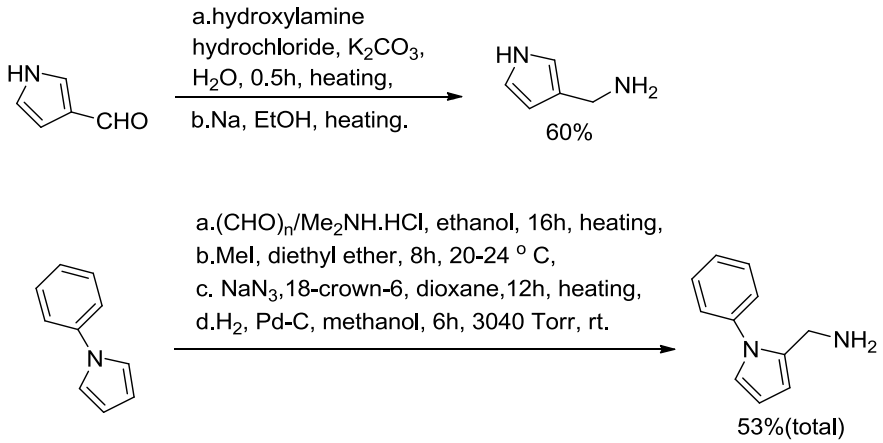
Scheme 5.11 Synthesis of TAK-438 and its derivatives

2. Methods to introduce the aminomethyl unit into pyrrole rings.

2.1. Traditional reductive amination

The current methods to access methanamine substituted pyrrole derivatives are mainly based on reductive amination of the corresponding pyrrole carboxaldehyde. For instance, the pyrrole carboxaldehyde can be converted to the oxime, which is then reduced (Scheme 5.12).[161]

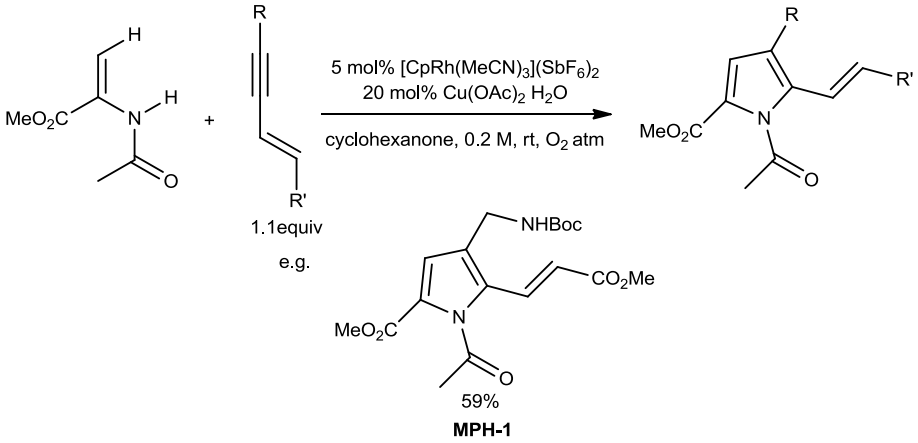
[161] (a) Korakas, D.; Varvounis, G. *Synthesis* **1994**, *2*, 164. (b) Katritzky, A. R.; Wang, J.; Yang, B. *Synth. Commun.* **1995**, *17*, 2631.



Scheme 5.12 Reductive amination

2.2. Rhodium-catalyzed pyrrole synthesis

Although, the aminomethyl group could be attached to the pyrrole ring *via* reductive amination of the carboxaldehyde precursors, they require multistep procedures to construct such pyrroles. Recently, Huestis and co-workers reported a rhodium-catalyzed approach to construct unsymmetrical 2,3-aliphatic-substituted indoles and pyrroles from simple nitrogen-containing starting materials and incorporated the aminomethyl in one single step. But only in one case, **MPH-1**, was *tert*-butylcarbamate-protected amine present at position 3 (Scheme 5.13).[162]



Scheme 5.13 Rhodium-catalyzed pyrrole synthesis

[162] Huestis, M. P., Chan, L., Stuart, D. R., Fagnou, K., *Angew. Chem., Int. Ed.*, **2011**, *50*,1338.

III. Radical synthesis of pyrroles

The lack of a general, modular and direct synthetic protocol to construct the aminoalkyl substituted pyrrole derivatives encouraged us to design new flexible routes to pyrroles related to TAK-438 and based on xanthate chemistry.[163] As was discussed previously the xanthate radical addition-transfer process allows many hitherto difficult inter- or intramolecular addition to olefins, and these transformations may be used for the construction of many heteroaromatic compounds.[164]

1. Previous applications of xanthate chemistry in pyrrole synthesis

The synthesis of highly substituted pyrroles remains challenging and only a limited numbers of examples dealing with metal-free, modular, and direct construction of the highly substituted pyrroles have been reported in the literature.[165] Several methods for the preparation of pyrroles have been developed in our group based on the chemistry of xanthates.

1.1. Radical reaction between enesulfonamides and *α*-xanthyl ketones

In 2002, we described the route to pyrroles presented in Scheme 5.14.[166] The enesulfonamide **FW-1** was readily prepared by the reaction between ethyl pyruvate and ethylsulfonamide. The radical reaction between this enamide **FW-1** and *α*-xanthyl

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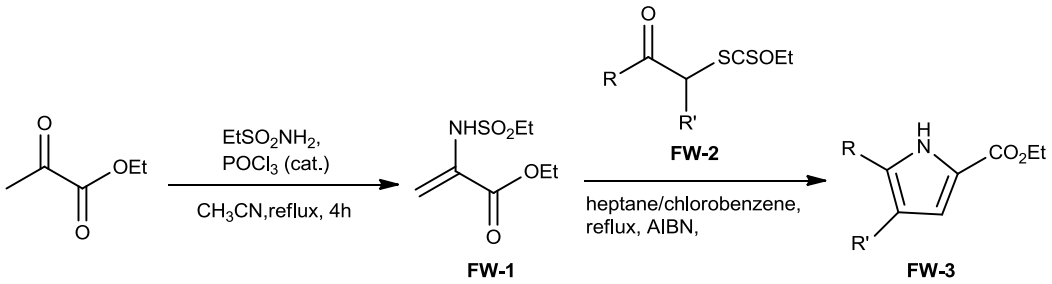
[163] (a) Zard, S. Z. *Angew. Chem., Int. Ed.* **1997**, *36*, 672. (b) QuicletSire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (c) Zard, S. Z. *Aust. J. Chem.* **2006**, *59*, 663. (d) Zard, S. Z. *Org. Biomol. Chem.* **2007**, *5*, 205. (e) Quiclet-Sire, B.; Zard, S. Z. *Pure Appl. Chem.* **2011**, *83*, 519.

[164] (a) El Qacemi, M.; Petit, L.; Quiclet-Sire, B.; Zard, S. Z. *Org. Biomol. Chem.* **2012**, *10*, 5707. (b) Jullien, H.; Quiclet-Sire, B.; Tétart, T.; Zard, S. Z. *Org. Lett.* **2014**, *16*, 302.

[165] (a) Zhao, M.-N.; Ren, Z. H.; Wang, Y. Y.; Guan, Z.-H. Org. Lett. **2014**, 16, 608. (b) Chen, F.; Shen, T.; Cui, Y.; Jiao, N. *Org. Lett.* **2012**, *14*, 4926.

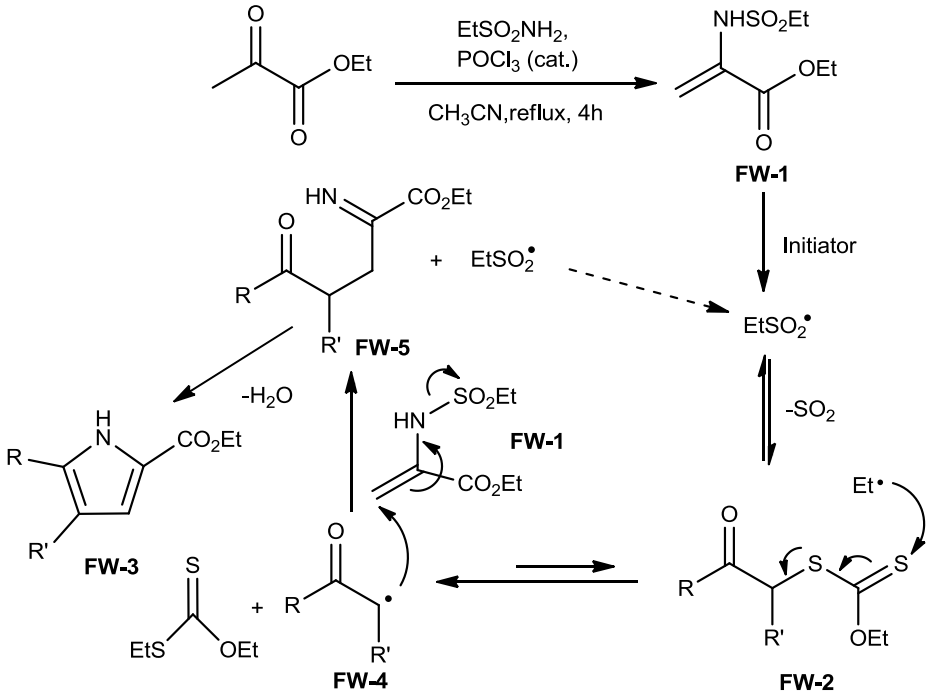
[166] Quiclet-Sire, B.; Wendeborn, F.; Zard, S. Z. *Chem. Commun.* **2002**, 2214.

ketones **FW-2** furnished an intermediate γ-keto imine which immediately underwent an intramolecular condensation to close the ring and form the corresponding pyrroles.



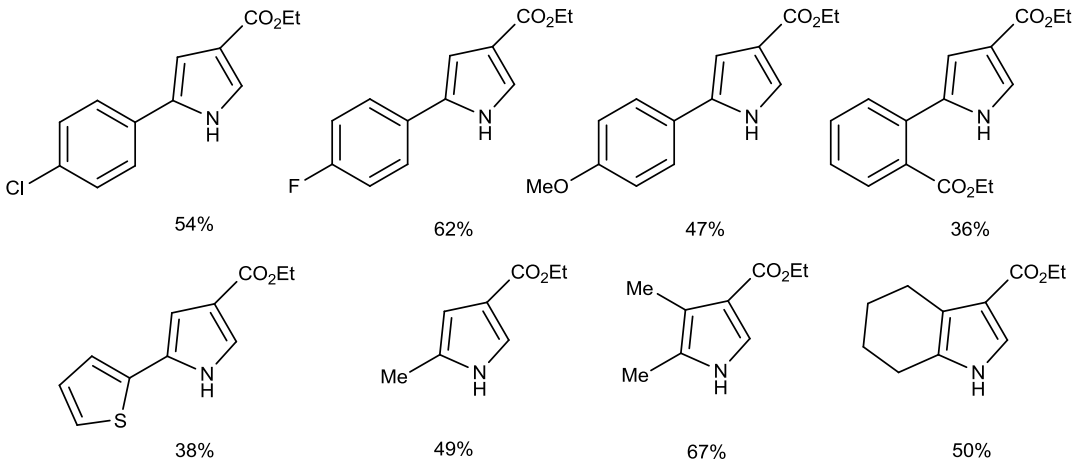
Scheme 5.14 Radical addition of enesulfonamides to α-xanthyl ketones

A plausible reaction pathway was proposed (Scheme 5.15). Under radical conditions, the addition-fragmentation on enesulfonamides **FW-1** occurs to generate an ethyl sulfonyl radical which loses sulfur dioxide to form an ethyl radical to propagate the chain. The ring closure of imine **FW-5** proceeds rapidly with loss of water to give the final pyrrole **FW-3**.



Scheme 5.15

The examples displayed in Scheme 5.16 demonstrate the tolerance for a wide range of functional groups. Furthermore, this method is ideal for accessing pyrroles bearing an ester group at position 4. However, the yields need to be improved if this method is to be applied on a large scale.

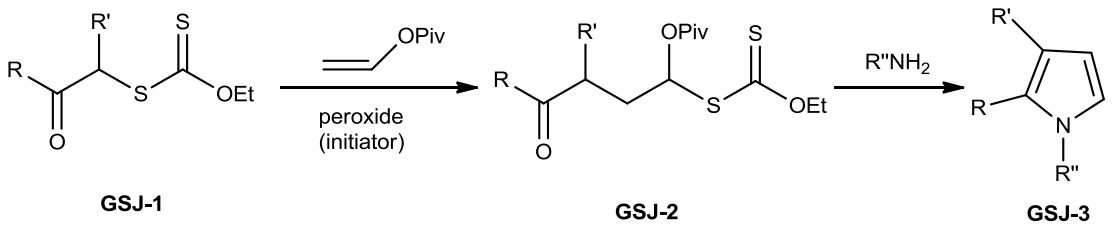


Scheme 5.16

1.2. Radical addition of *α*-xanthyl ketones to vinyl pivalate

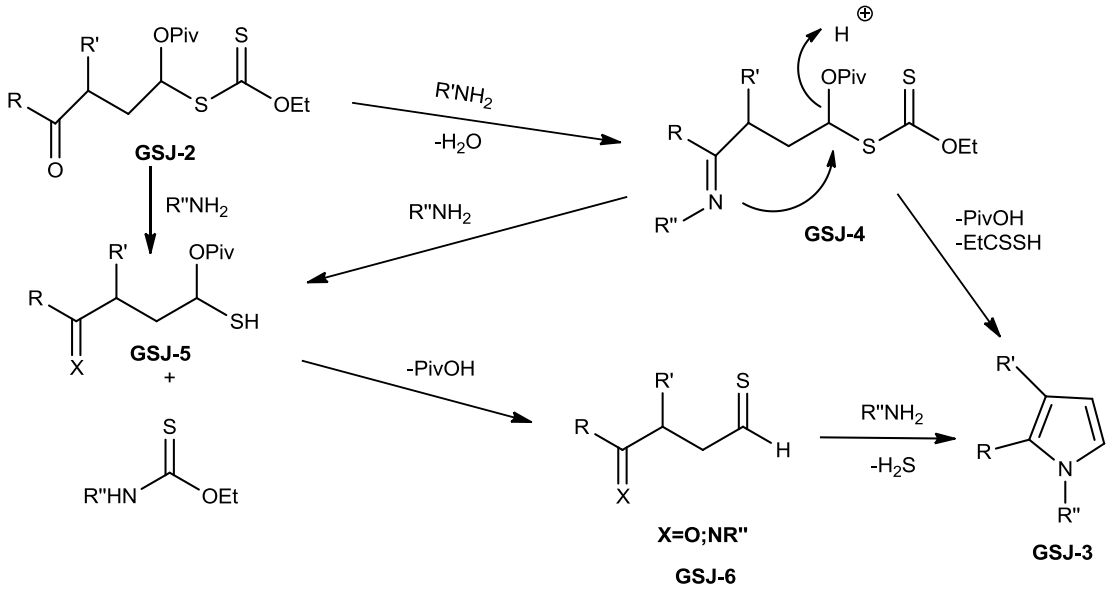
In the same year, the radical addition of *α*-xanthyl ketones to vinyl pivalate followed by aminolysis to pyrroles was described (Scheme 5.17).[167] Adducts **GSJ-2** obtained from the radical addition may be considered as the synthetic equivalents of 1,4-ketoaldehydes, which were used to form pyrroles by the Paal-Knorr reaction.

[167] Quiclet-Sire, B., Quintero, L., Sanchez-Jimenez, G., Zard, S. Z. *Synlett.* **2003**, *1*, 75.



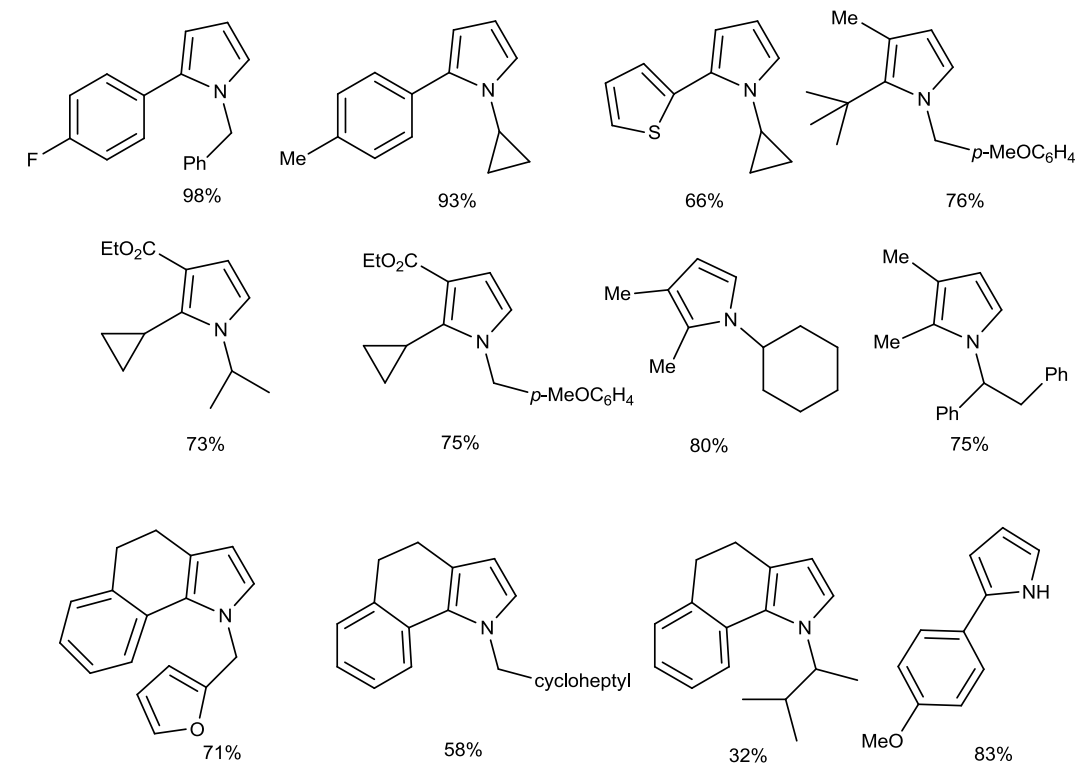
Scheme 5.17 Radical addition of α-xanthyl ketones to vinyl pivalate

Two plausible mechanistic pathways are displayed in Scheme 5.18. In the first pathway, the condensation of the amine with ketones **GSJ-2** gives the intermediate **GSJ-4** followed by its ring closure to afford the corresponding pyrrole **GSJ-3**. The second pathway derives from the possibility of aminolysis of the xanthate to give intermediate **GSJ-5** then thioaldehyde **GSJ-6** which can furnish the same pyrrole **GSJ-3** by a variety of Paal-Knorr reaction.



Scheme 5.18

The examples assembled in Scheme 5.19 indicate that 2-substituted or 2,3-disubstituted pyrroles bearing various functional groups can be readily available in generally high yield by this route.



Scheme 5.19

1.3. Radical synthesis of complex 1,4-diketones

1,4-diketones are of major importance for the synthesis of valuable heteroaromatic compounds such as thiophenes,[168] furans,[169] and pyrroles[170] via the Paal-Knorr synthetic pathway. A powerful modular approach for the preparation of complex 1,4-diketones was descried in our group, which could be applied in designing pyrrole synthesis (Scheme 5.20).[171] The radical addition of α-xanthyl ketones to 2-fluoro-6-pyridinyloxy derivatives afforded 1,4-diketones *via* an

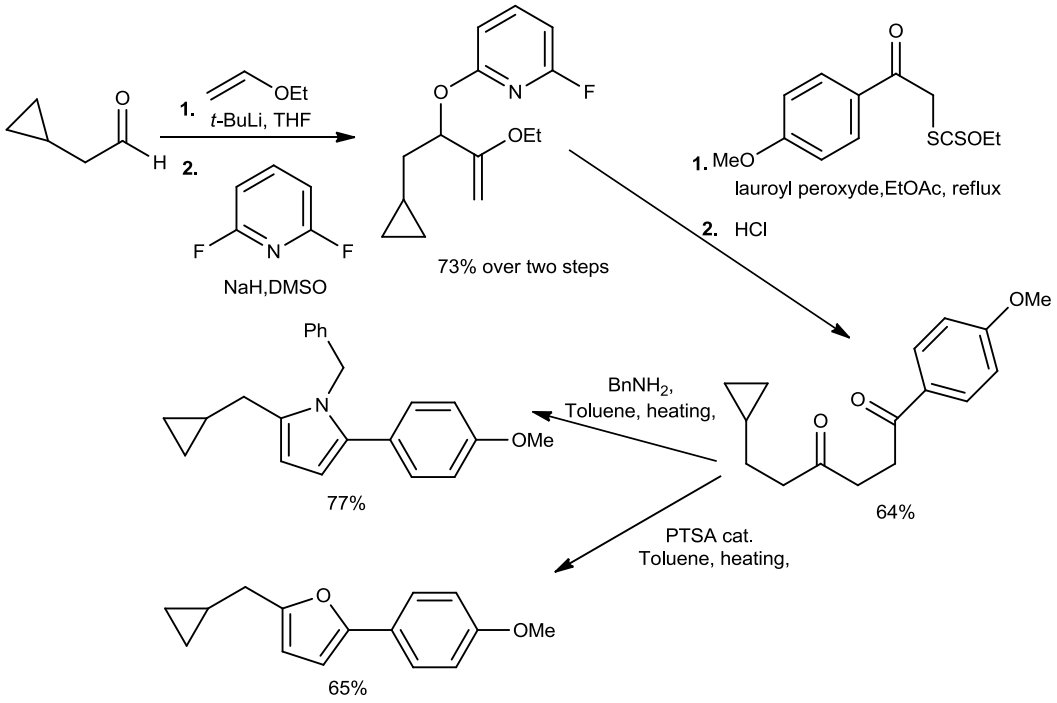
[168] Russell, R. K. In *Comprehensive Heterocyclic Chemistry II;* Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds; Pergamon Press: Oxford, 1997; Vol. 2, pp 679-729.

[169] (a) Dean, F. M. *Naturally Occurring Oxygen Ring Compounds;* Butterworths: London, 1963; Chapter 1, p 1. (b) Elliot, M. C. *J. Chem. Soc., Perkin Trans. I* **2002**, 2301. (c) Harmange, J. C.; Figadere, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711.

[170] (a) Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2005**, 5277. (b) Minetto, G.; Raveglia, L. F.; Tadde, M. *Org. Lett.* **2004**, *6*, 389. (c) Veitch, G. E.; Bridgwood, K. L.; Rands-Trevor, K.; Ley, S. V. *Synlett* **2008**, *17*, 2597.

[171] Debien, L., Quiclet-Sire, B., Zard, S. Z. *Org. Lett.* **2011**, *13*, 5676.

addition-fragmentation pathway and construction with an amine or ammonia provides the corresponding pyrroles.[172] A broad range of functional groups are tolerated in this simple process and the yields are generally high.



Scheme 5.20 Synthesis of 1,4-diketones and pyrroles

2. Pyrrole synthesis based on radical addition of various *α*-xanthyl ketones to *N*-Boc-protected azetine

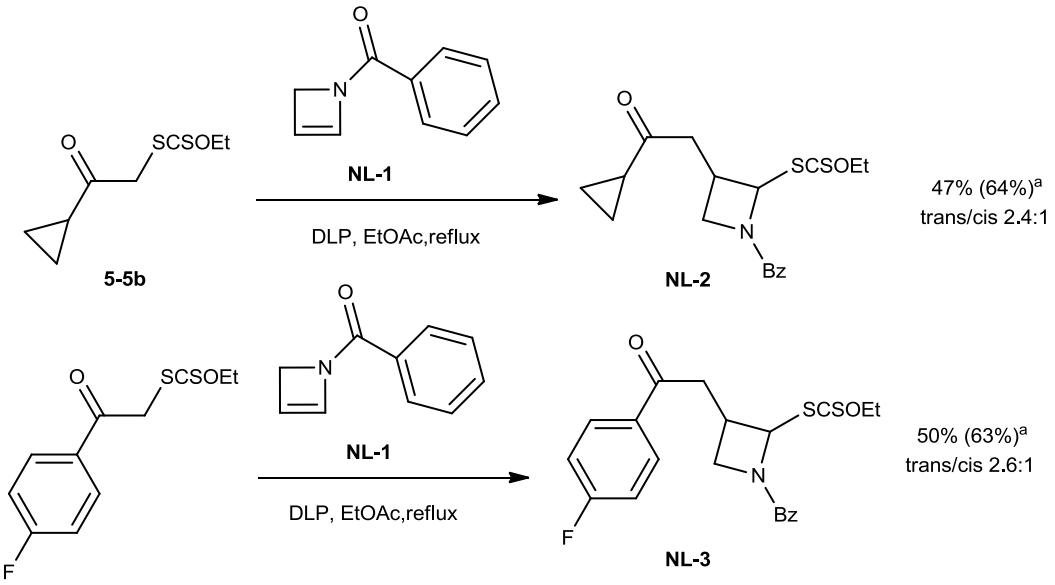
In continuation of the work on pyrrole synthesis, we adapted the approach using xanthates to access pyrroles related to TAK-438.

2.1. Synthesis of *N*-protected azetine

A few years ago, we observed that the radical addition of xanthates to various strained olefins could afford corresponding adducts in good yield.[173] A protected

[172] Braun, M. G.; Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **2011**, *133*, 15954.

azetine was one of the strained olefins that were examined at the time (Scheme 5.21).



[a] Yields in brackets are based on recovered starting material.

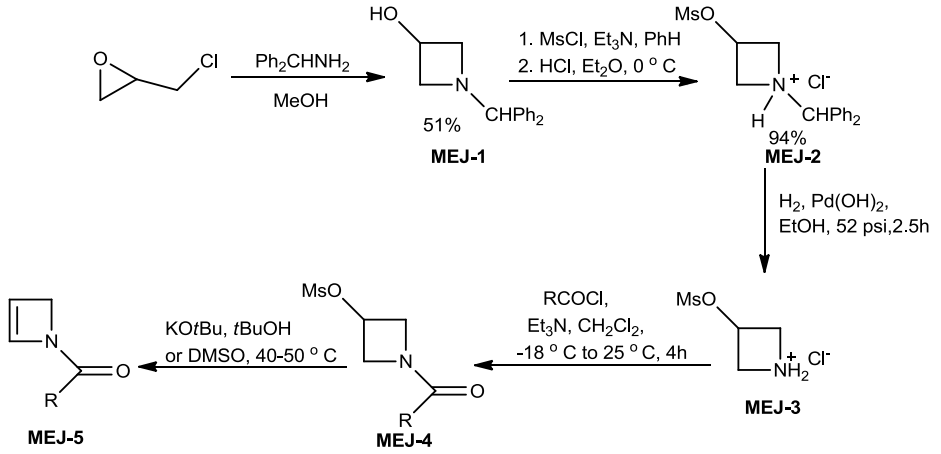
Scheme 5.21 Radical addition of xanthates to azetine

The preliminary study summarized in Scheme 5.21 encouraged us to further explore this possibility to synthesize TAK-438 type pyrroles.

In 1991, Jung and co-workers proposed an efficient synthetic route to 1-acyl-2-azetines (Scheme 5.22).[174] The nucleophilic attack on the epoxide of epichlorohydrin by benzhydrylamine gives the ring opening intermediate and then its cyclization affords the corresponding azetidine product **MEJ-1**. The sulfonylation of **MEJ-1** gives **MEJ-2**. Next, the reduction of **MEJ-2** affords **MEJ-3** which is then protected by various acyl groups to form **MEJ-4.** Finally, the elimination of its methanesulfonyl group furnishes the desired *N*-protected azetine **MEJ-5**.

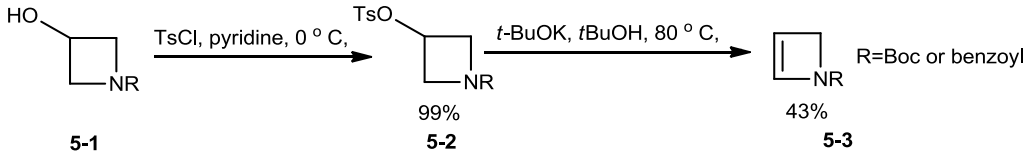
[173] Legrand, N.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **2000**, *41*, 9815.

[174] Jung, M. E.; Choi, Y. M. *J. Org. Chem.* **1991**, *56*, 6729



Scheme 5.22 Synthesis of 1-acyl-2-azetines

Since 3-hydroxyazetidine and *N*-Boc-3-hydroxyazetidine were commercially available from Fluorochem.,[175] the preparation of *N*-protected azetines now has been simplified, and the transformation of *N*-benzoyl- or *N*-*Boc*-3-hydroxyazetines to *N*-protected azetidines was accomplished via a sequential two step-sulfonylation and elimination (Scheme 5.23).[176]



Scheme 5.23 Synthesis of *N*-protected azetines

2.2. Radical synthesis of 2-disubstituted *N*-Boc-protected 4-aminomethyl-pyrroles

The typical radical addition of xanthates to *N*-protected azetines was then examined by us. According to the previous study, the addition of xanthates to *N*-benzoyl-azetine gave the desired adducts in moderate yield; however, under the

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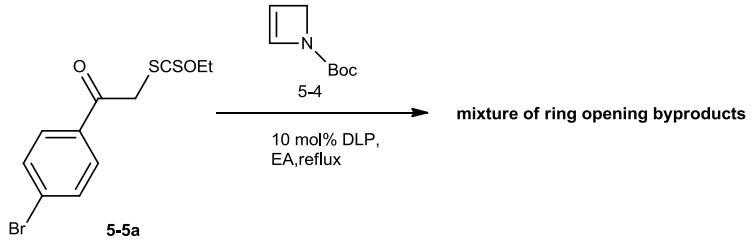
[175] 3-Hydroxyazetidine (25 g, 32 £) and *N*-*Boc*-3-hydroxyazetidine (25 g, 78 £).

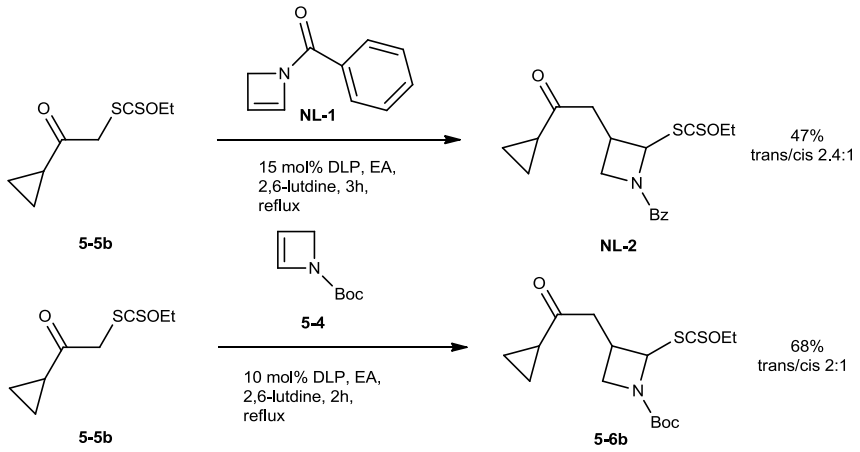
[176] McDonald, R. I., Wong, G. W., Neupane, R. P., Stahl, S. S., Landis, C. R., *J. Am. Chem. Soc.* **2010**, *132*, 14027.

same condition, the addition of xanthate **5-5a** to *N*-Boc-azetine **5-4** gave a mixture of ring opening byproducts instead of the desired adduct (Scheme 5.24). We considered that the slightly stronger basicity of *N*-Boc-azetine compared to *N*-benzoyl-azetine made the adducts more sensitive to mild acidic conditions. Thus, even a quite small amount of lauric acid formed by the decomposition of lauroyl peroxide may result in the opening of azetidine ring to release the ring strain.



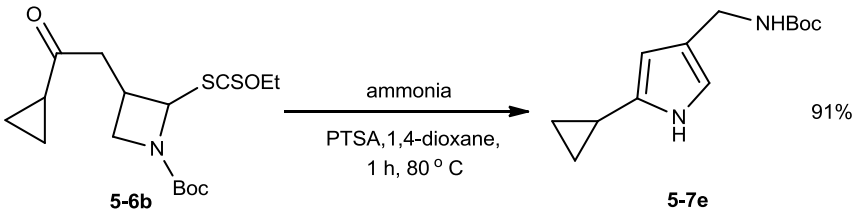
Scheme 5.24

The solution was to add some mild, hindered base such as 2,6-lutidine to the solution to neutralize the slightly acidic environment. We were delighted to observe that under these conditions the radical addition of xanthate **5-5b** to *N*-Boc-protected azetine **5-4** gave desired adduct **5-6b** in good yield (Scheme 5.25). In contrast with *N*-benzoyl-protected azetine, less DLP and a shorter reaction time was needed for the radical addition and the adduct **5-6b** was obtained in higher yield. We next examined the formation of a pyrrole from adduct **5-6b**.



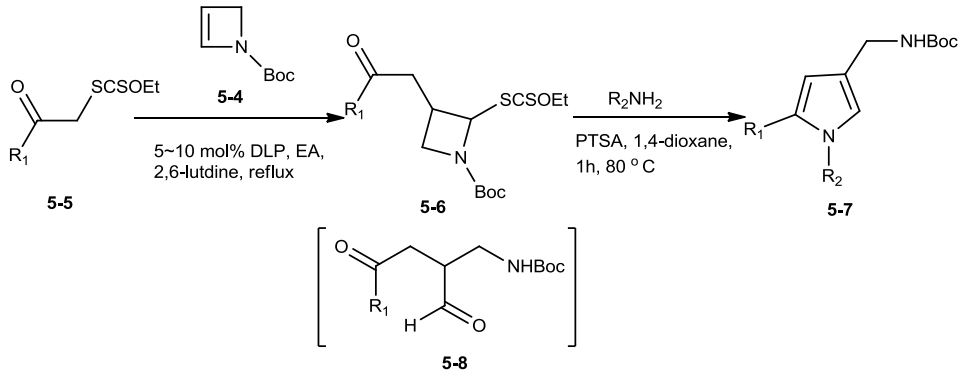
Scheme 5.25 Radical addition of xanthate **5-5b** to *N*-protected azetine

Indeed, aminolysis of **5-6b** by ammonia under similar conditions used previously resulted in the formation of desired pyrrole **5-7e** in high yield (Scheme 5.26).



Scheme 5.26 Aminolysis of adduct **5-6b**

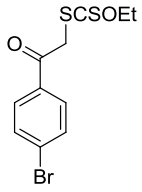
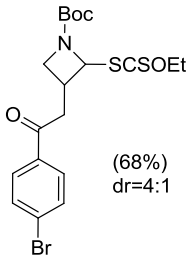
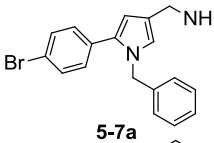
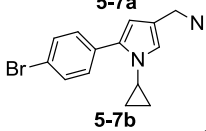
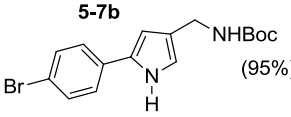
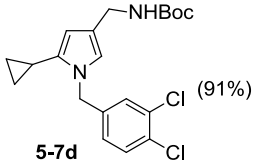
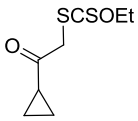
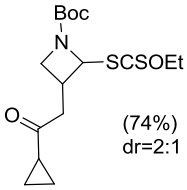
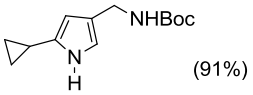
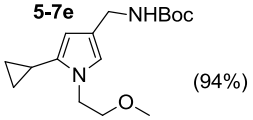
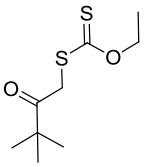
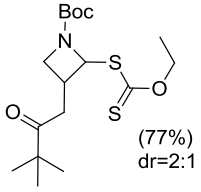
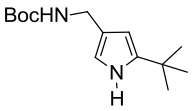
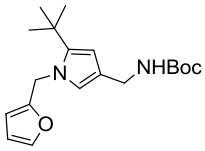
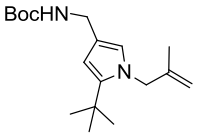
With this first success in hand, we proceeded to explore the scope of this new synthesis of pyrroles (Scheme 5.27).



Scheme 5.27 Synthesis of pyrroles **5-7** using a modular approach

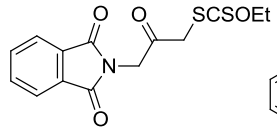
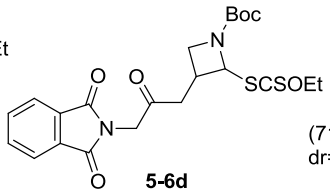
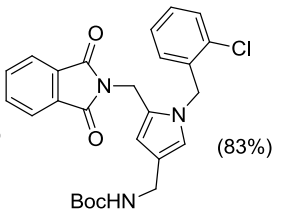
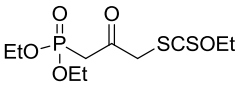
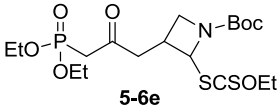
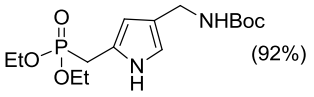
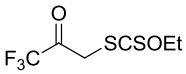
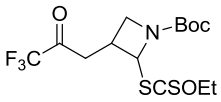
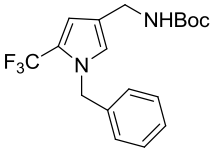
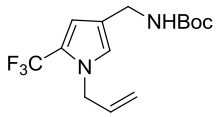
A wide range of α-ketonyl xanthates **5-5** bearing different functional groups underwent the radical addition with azetine **5-4** to afford adducts **5-6** in generally good yield, as shown by the results in Table 5.1. Treatment of the adducts with various primary amines or ammonia furnished the corresponding pyrroles **5-7** very efficiently within a short reaction time (ca 1h).

Table 5.1 Examples of pyrrole **5-7**

Xanthate **5-5**	Adduct **5-6** (yield%)[a]	Amine	Pyrrole **5-7** (yield%)
 **5-5a**	 (68%) dr=4:1 **5-6a**	benzylamine	 **5-7a** (87%)
		cyclopropylamine	 **5-7b** (93%)
		ammonia	 **5-7c** (95%)
		3,4-dichloro-benzylamine	 **5-7d** (91%)
 **5-5b**	 (74%) dr=2:1 **5-6b**	ammonia	 **5-7e** (91%)
		2-methoxyethylamine	 **5-7f** (94%)
 **5-5c**	 (77%) dr=2:1 **5-6c**	ammonia	 **5-7g** (82%)
		furfurylamine	 **5-7h** (92%)
		2-methylallylamine	 **5-7i** (88%)

[a] The dr was measured by NMR spectroscopy after purification by column chromatography.

Table 5.1 Examples of pyrrole **5-7** (continued)

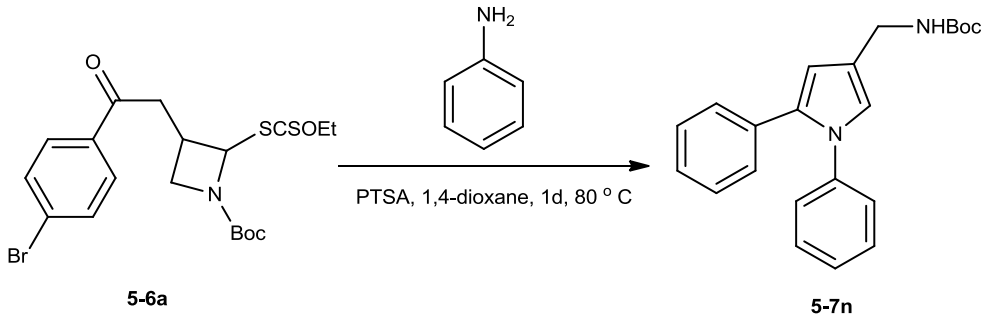
Xanthate **5-5**	Adduct **5-6** (yield%)[a]	Amine	Pyrrole **5-7** (yield%)
 **5-5d**	 **5-6d** (71%) dr=4:1	(2-chlorophenyl) methanamine	 **5-7j** (83%)
 **5-5e**	 **5-6e** (68%) dr=2:1	ammonia	 **5-7k** (92%)
 **5-5f**	 **5-6f**	benzylamine	 **5-7l** (63%)[b]
		allyamine	 **5-7m** (68%)[b]

[a] The dr was measured by NMR spectroscopy after purification by column chromatography.
[b] Over all total yield for the two steps.

The variety of the pyrroles is shown in Table 5.1. By placing various functional groups on the *α*-ketonyl xanthates, aryl, cyclopropyl, *tert*-butyl, phosphonomethyl, allyl and even trifluoromethyl groups can be incorporated into the final pyrroles. It is worth noting that pyrrole **5-7k** bearing a phosphonyl motif may further undergo the Horner–Wadsworth–Emmons reaction; the pharmacologically interesting trifluoromethyl group was easily introduced into pyrroles **5-7l** and **5-7m**. The synthesis of fluorinated pyrroles is rarely a trivial problem. In the case of pyrrole **5-7j**, two aminomethyl groups having different *N*-protecting groups are present.

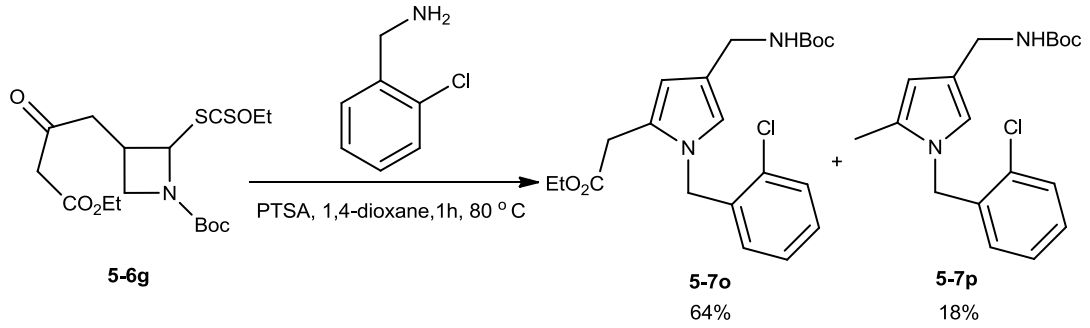
The aminolysis of xanthate group by anilines such as **5-6a** was also briefly investigated, using the same experimental conditions. However, due to the weak nucleophilicity of the aniline, only a small amount of corresponding pyrrole product

5-7n could be observed by NMR spectrum. Even after one day most of the starting material **5-6a** remained in the solution (Scheme 5.28).



Scheme 5.28 Aminolysis of **5-6a** by aniline

In the case of pyrrole **5-7o**, we found a mixture of a small amount of the desired pyrrole **5-7o** and a large quantity of byproducts which was appeared to result from aminolysis of its ester group. To minimize those byproducts, one equivalent of *p*-TsOH was added to lock the aminolysis of the ester (Scheme 5.29). The yield of pyrrole **5-7o** was significantly increased, but a small amount of pyrrole **5-7p** was also formed *via* an acid-catalyzed deethoxycarboxylation process.

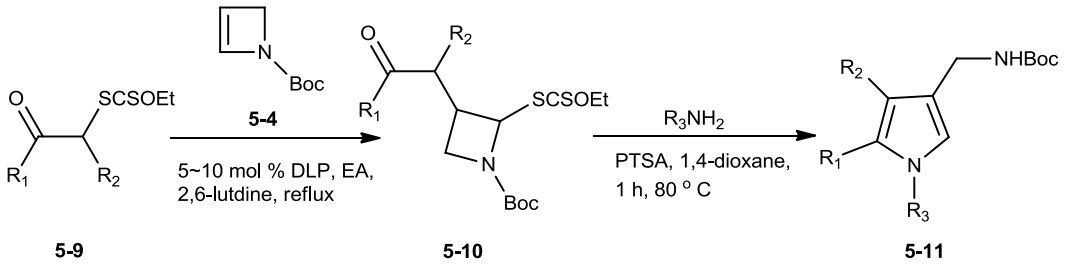


Scheme 5.29 Aminolysis of adduct **5-6g**

2.3. Radical synthesis of 2,3-trisubstituted and polycyclic *N*-Boc-protected 4-aminomethyl-pyrroles

To extend the scope of this method we used secondary *α*-ketonyl xanthates as the starting materials. The addition of secondary *α*-ketonyl xanthates **5-9** to *N*-protected

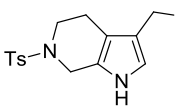
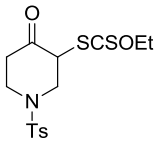
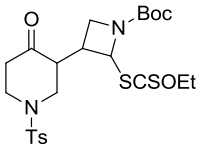
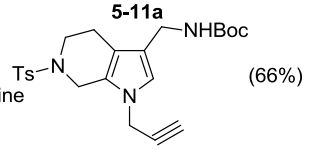
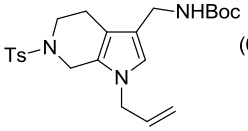
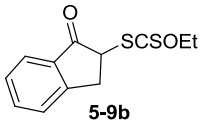
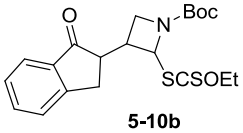
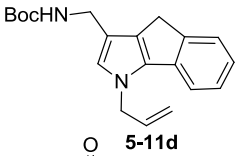
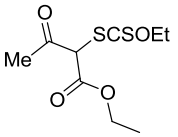
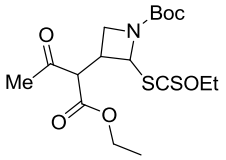
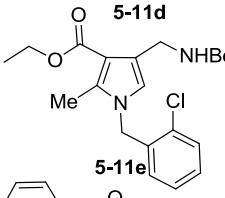
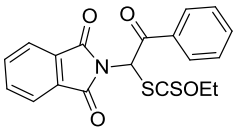
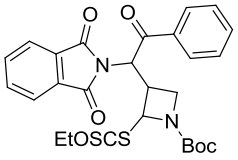
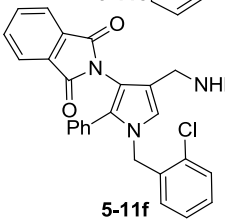
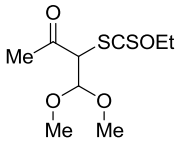
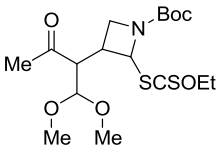
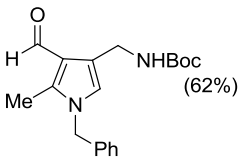
azetine **5-4** indeed afforded adducts **5-10** in high yield (Scheme 5.30 and Table 5.2). However, since this radical addition led to the formation of four diastereoisomers, the crude reaction mixture was purified by a quick filtration on silica gel to obtain the pure mixture of the four diastereoisomers which was then engaged in the next step to form the corresponding pyrroles **5-11** with the same overall efficiency.



Scheme 5.30 Synthesis of 2,3,4-trisubstituted and polycyclic pyrrole **5-11**

The examples listed in Table 5.1 are for 2,4-disubtituted pyrroles, while those in Table 5.2 are for 2,3,4-trisubstituted polycyclic pyrrole derivatives. A similar variety of functional groups may be introduced into the latter. Bicycle pyrroles such as **5-11** (**a, b, c**) with a fused six-membered including a piperidine ring and tricyclic structures were easily constructed. Under the acidic conditions, the acetal in adduct **5-10e** was cleared to afford pyrrolecarboxaldehyde **5-11g** directly. This interesting pyrrole could in principal be elaborated into a more complex 3,4-bis-(aminomethyl)pyrroles by reductive amination. Alternatively, the aldehyde may be condensed with the amino group already present following removal of the protecting Boc group. In pyrrole **5-11f**, a phthalimide protected amino unit is directly attached onto the ring. Very few methods allow the synthesis of amino pyrroles, which are almost invariably obtained by reduction of the corresponding nitropyrrole. Furthermore, in contrast with sensitive free amino pyrroles, the electron-withdrawing phthalimido a motif protects the pyrrole against aerial oxidation.

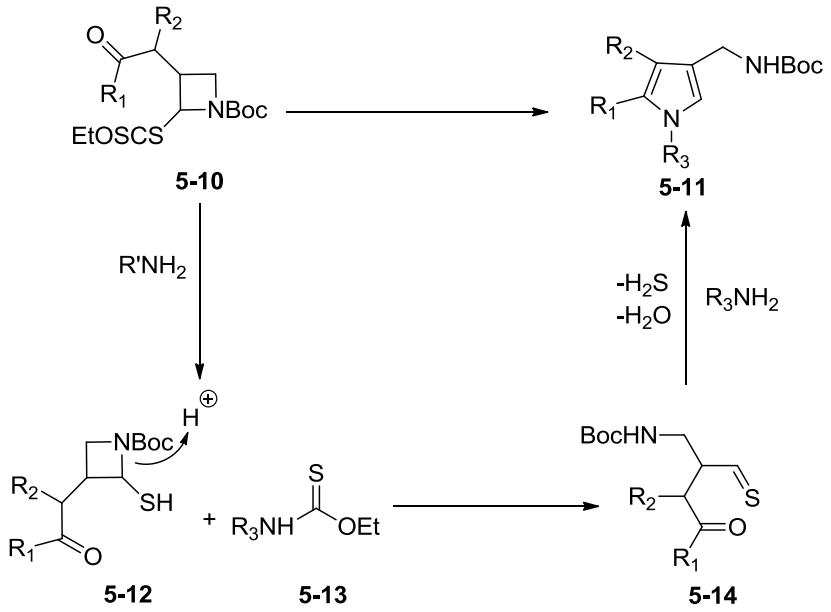
Table 5.2 Examples of Pyrrole **5-11**

Xanthate **5-9**	Adduct **5-10**[a]	Amine	Pyrrole **5-11** (yield%)[b]
		ammonia	 **5-11a** (67%)
 **5-9a**	 **5-10a**	mono-propargylamine	 **5-11b** (66%)
		allylamine	 **5-11c** (63%)
 **5-9b**	 **5-10b**	allylamine	 **5-11d** (68%)
 **5-9c**	 **5-10c**	(2-chlorophenyl) methanamine	 **5-11e** (61%)
 **5-9d**	 **5-10d**	(2-chlorophenyl) methanamine	 **5-11f** (58%)
 **5-9e**	 **5-10e**	Benzylamine	 **5-11g** (62%)

[a] The crude adducts were used directly in second step after a quick purification on silica gel. [b] The total yield of step 1 and step 2.

A plausible mechanism for the pyrrole formation is outlined in Scheme 5.31. Aminolysis of the xanthate leads to the formation of thiol **5-12** and thiocarbamate **5-13**, which in some cases could be isolated. Next, due to the strain of the azetidine

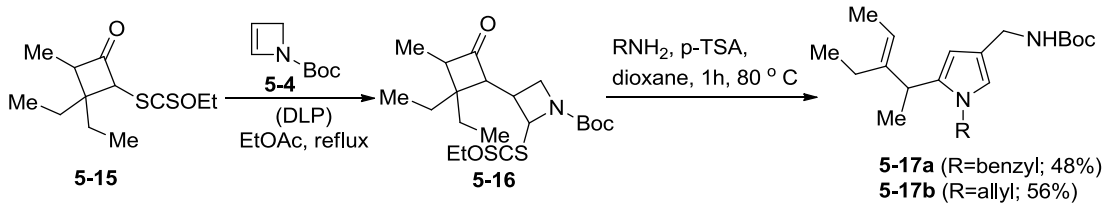
ring thiol **5-12** readily undergoes ring opening to form thioaldehyde **5-14**. Finally, since thioaldehyde **5-14** bearing a thiocarbonyl and a carbonyl groups, its condensation with primary amines or ammonia gives the corresponding pyrrole **5-11** by a similar pathway to the one involved in the Paal-Knor reaction.



Scheme 5.31 Mechanism of pyrrole formation

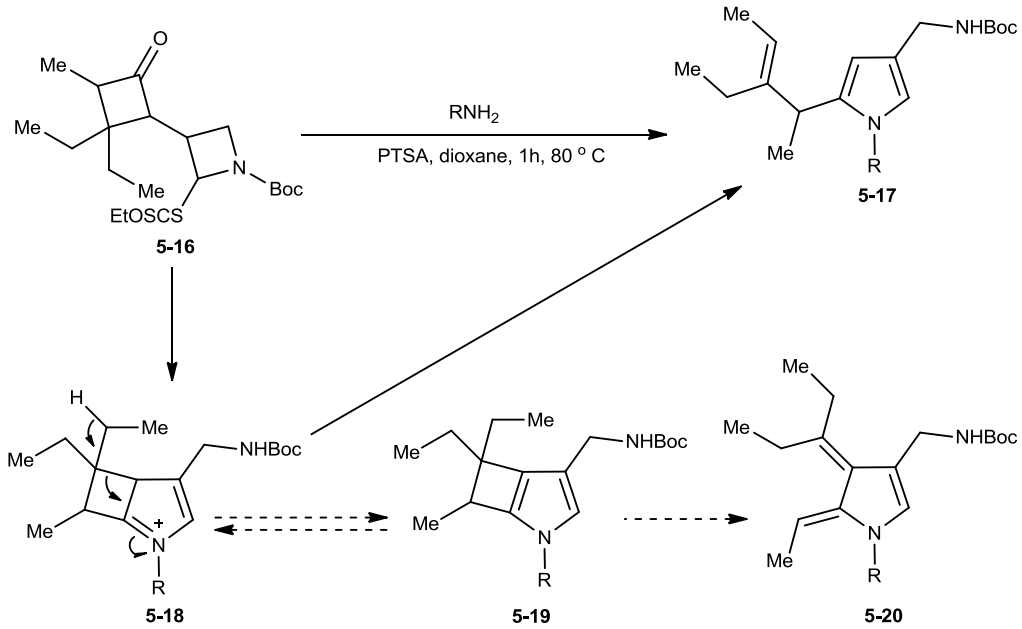
We attempted to prepare a pyrrolocyclobutanone using the same approach. Only two cases for the synthesis of such pyrroles had been reported so far.[177] The radical addition of xanthate **5-15** to **5-4** proceeded normally to give **5-16** by further aminolysis with two different amines furnished unexpected pyrroles **5-17a** and **5-17b**, where the cyclobutane ring had been broken (Scheme 5.32).

[177] (a) Buhr, G. *Chem. Ber.* **1973**, *106*, 3544. (b) Yamasaki, K.; Saito, I.; Matsuura, T. *Tetrahedron Lett.* **1975**, *16*, 313. One diene of type 11 has been generated and captured via a Diels−Alder cycloaddition: (c) Janicki, S. Z.; Petillo, P. A.; Vessels, J. T. *Org. Lett.* **2000**, *2*, 73.



Scheme 5.32 Synthesis of pyrroles **5-17**

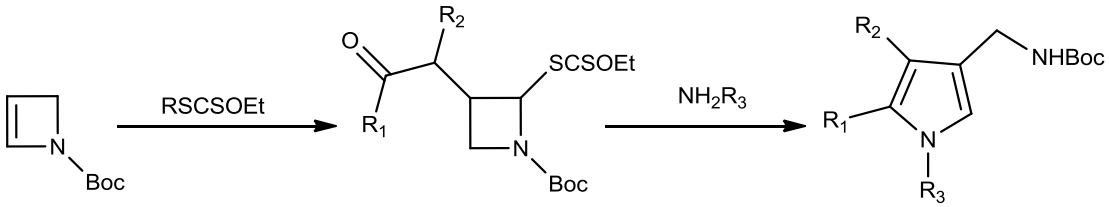
A plausible explanation is that upon treatment of adduct **5-16** with the primary amine and *p*-toluenesulfonic acid, a cyclic intermediate **5-18** is indeed formed, but the strain inherent in the pyrrolocyclobutanone structure force the reaction to proceed by ring opening of the cyclobutane in the final aromatization step leading to pyrrole **5-17**, as shown in Scheme 5.33. It is not clear if intermediate **5-18** exists in the medium in equilibrium with the aromatic pyrrole **5-19**, the latter could in principle undergo an electrocyclic ring opening to give **5-20**, but no products derived from such an intermediate were observed.



Scheme 5.33 Mechanism for the formation of pyrrole **5-17**

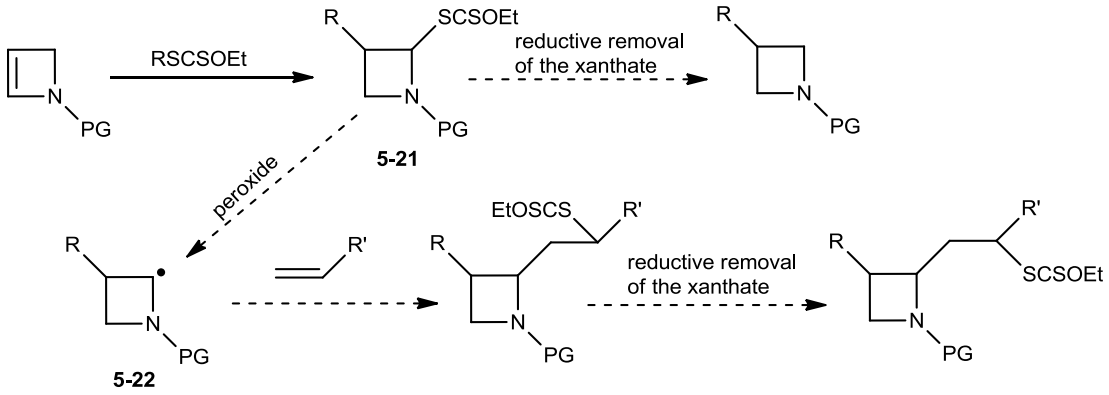
Conclusion

In summary, we have established a flexible, convergent route for the synthesis of diversely substituted pyrroles related to TAK-438. This two-step modular procedure generalized in Scheme 5.34 represents a practical approach to quickly combine these components into a pyrrole structure. Almost any functional group could be incorporated either through the xanthate partner or through the amine moiety. Most of the pyrroles obtained in the present study would be tedious to prepare by other routes based on ionic or organometallic pathways.



Scheme 5.34

Two possible extensions of this approach are outlined in Scheme 5.35. Reductive removal of the xanthate group from adducts **5-21** leads to variously functionalized azetidine derivatives which are gaining importance in medicinal chemistry. The addition of intermediate xanthate **5-21** to another olefin would also be interesting. This has not yet been attempted but may require changing the protecting group to tune the stability of the intermediate radical **5-22**. In addition to providing a better understanding of the influence of the substituents on the nitrogen on the stability of the radicals, such an extension would open access to highly substituted azetidine derivatives.


RSCSOEt
SCSOEt
reductive removal
of the xanthate
PG
5-21
peroxide
5-22
R'
EtOSCS
reductive removal
of the xanthate
SCSOEt

Scheme 5.35