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Synthesis of Multisubstituted Furans, Pyrroles, and Thiophenes via Ynolates

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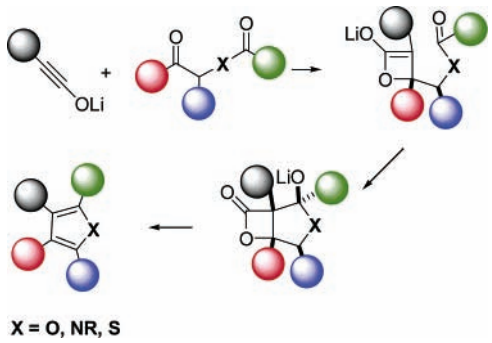
ABSTRACT



An efficient synthetic method for the preparation of multisubstituted furans, thiophenes, and pyrroles using ynolates was developed. This novel formal [4 + 1] annulation by C2–C3 and C3–C4 bond formations includes cycloaddition, cyclization, decarboxylation, and dehydration as key steps.

Furans, pyrroles, and thiophenes are frequently encountered components of natural products and of compounds used in medicine and material sciences.[1] Efficient synthetic methods for these heterocycles consequently are highly desirable for the construction of these compounds. Although numerous methods for syntheses of heterocycles have been reported, they can generally be categorized as 1−2 and/or 1−5 bond connections, such as the Paal−Knorr synthesis,[2] 1−2 and/or 3−4 bond connections,[3] 2−3 and 4−5 connections,[4] and so on (Figure 1).[5] However, efficient short-step methods for the construction of unsymmetrical multisubstituted heterocycles are limited by the preparation of substituted starting materials and by steric congestion, which the cyclization must

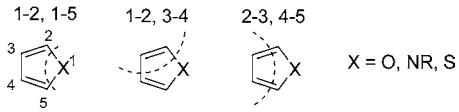


Figure 1. Representative category of the synthesis of heterocycles.

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(1) For reviews, see: (a) *Comprehensive Heterocyclic Chemistry II*; Katrizky, A. R., Rees, C. W., Scriven, E. F., Eds.; Pergamon: Oxford, 1996; Vol. 2. (b) Walsh, C.; Garneau-Tsodikova, S.; Howard-Jones, A. R. *Nat. Prod. Rep.* **2006**, *23*, 517−531. (c) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753−1783.

(2) (a) Knorr, L. *Ber.* **1884**, *17*, 1635. (b) Paal, C. *Ber.* **1885**, *18*, 367−371.

(3) For a recent example, see: Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074−2075.

(4) For a recent example, see: Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260−9266.

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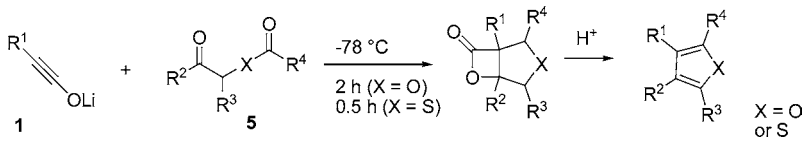
Table 1. Synthesis of Furans and Thiophenes



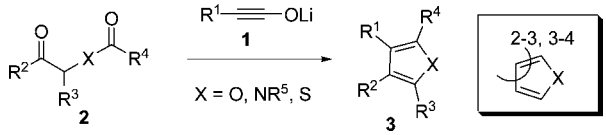
entry	1	R^1	5	R^2	R^3	R^4	X	method[a]	products	yield (%)
1	**1a**	Me	**5b**	Ph	Me	Me	O	A	**10**	70
2	**1a**	Me	**5c**	Ph	Me	Ph	O	A	**11**	84
3	**1a**	Me	**5c**	Ph	Me	Ph	O	B	**11**	77
4	**1a**	Me	**5d**	Ph	Me	4-pentenyl	O	A	**12**	66
5	**1a**	Me	**5e**	Ph	Ph	Ph	O	A	**13**	42
6	**1b**	Bu	**5b**	Ph	Me	Me	O	A	**14**	83
7	**1a**	Me	**5f**	Ph	Me	Me	S	C	**15**	90
8	**1a**	Me	**5g**	Ph	Me	Ph	S	C	**16**	85
9	**1a**	Me	**5h**	Ph	H	Me	S	C	**17**	84
10	**1a**	Me	**5i**	Ph	Me	2-thienyl	S	C	**18**	66
11	**1a**	Me	**5j**	Ph	Me	(*E*)-styryl	S	D	**19**	90
12	**1a**	Me	**5k**	Et	Me	Ph	S	C	**20**	93
13	**1a**	Me	**5l**	2-thienyl	Me	Ph	S	*b*	**21**	71

[a] Decarboxylation, A: TsOH (0.1 equiv) in benzene under reflux; B: one-pot reaction (see text); C: TsOH (1 equiv) in toluene under reflux; D: reflux in xylene without acid. [b] Direct formation of thiophene (see text).

overcome.[6] A new category of synthesis that addresses these concerns is therefore needed.

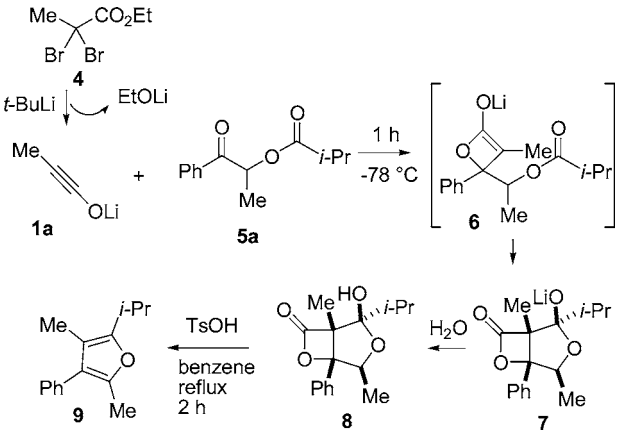
Ynolates **1** are ketene anion equivalents, which initiate sequential one-pot reactions.[7] Since ynolates are compact linear-shape carbanions, they can react with even sterically hindered substrates, leading to multisubstituted products.[8] Herein, we describe a novel methodology for the efficient synthesis of multisubstituted furans, pyrroles, and thiophenes **3** using ynolates **1** with α-acyloxy-, α-acylamino-, and α-acylthioketones **2** via a method of the category of the 2−3 and 3−4 bond connection (Scheme 1).[9]

Scheme 1



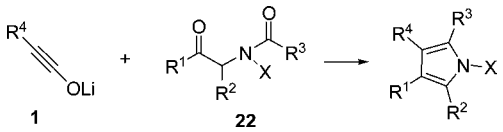
In the torquoselective olefination of α-acyloxyketone **5** via the ynolate **1a**,[10] we discovered a small amount of a less polar side product, the tetrasubstituted furan **9**. In order to elucidate the mechanism, we tried to isolate the reaction intermediates. When the reaction of the acyloxyketone **5a** with the ynolate **1a**, prepared from α,α-dibromo ester **4** with *t*-BuLi, was carried out at −78 °C and quenched for 30 min, an intermediate was obtained in good yield as a single isomer (Scheme 2). Its structure was found to be the fused *β*-lactone **8**,[11] which was considered to form via cycloaddition of **1a** and **5a**, followed by cyclization of the resulting enolate **6**. This intermediate **8** was treated with TsOH in benzene under reflux to afford the tetrasubstituted furan **9** via decarboxylation and dehydration. Using this protocol, we then synthesized several types of tetrasubstituted furans. The initial cycloaddition was complete within 1 h at −78 °C, and the resulting fused *β*-lactones, without purification, were decarboxylated under reflux in benzene in the presence of TsOH (0.1 equiv) to provide the furans. As shown in Table 1 (entries 1−6), aliphatic and aromatic groups can be used as R^2−R^4. This reaction can be carried out in one pot by addition of an excess of TsOH into the reaction mixture after the formation of the fused *β*-lactone (entry 3). α-Acylthioketones also afforded multisubstituted thiophenes via the

Scheme 2



(5) For recent examples, see: (a) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468−469. (b) Jung, C-K.; Wang, J-C.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4118−4119.

Table 2. One-Pot Synthesis of Pyrroles



entry	1	R^4	22	R^1	R^2	R^3	X	method[a]	product	yield (%)
1	**1a**	Me	**22b**	Ph	Me	Ph	Bn	C	**27**	67
2	**1a**	Me	**22c**	Ph	Me	*i*-Pr	Bn	A	**28**	65
3	**1a**	Me	**22d**	Ph	Me	CF_3	Bn	B	**29**	71
4	**1a**	Me	**22e**	Ph	Me	*t*-Bu	allyl	A	**30**	49
5	**1c**	*i*-Pr	**22a**	Ph	Me	Ph	PMP	C	**31**	75
6	**1d**	Ph	**22a**	Ph	Me	Ph	PMP	C	**32**	59
7	**1a**	Me	**22f**	Pr	Et	Ph	PMP	C	**33**	67
8	**1a**	Me	**22g**	-$(CH_2)_4$-		Ph	Bn	D	**34**	71
9	**1a**	Me	**22h**	Ph	Me	CO_2Et	allyl	C	**35**	36
10	**1a**	Me	**22i**	Ph	Me	Ph	OMP[c]	A	**36**	83
11	**1a**	Me	**22k**	Ph	H	Ph	PMP	A[b]	**37**	70

[a] A: at −20 °C for 2−3 h; B: after method A, the β-lactone was treated with TsOH (0.1 equiv) under reflux in toluene; C: at 0 °C for 1−3 h; D: after method C, the β-lactone was treated with TsOH (0.1 equiv). [b] Phenyl dibromopropionate was used as the precursor of the ynolate. BuLi (1 equiv) was added after the formation of the β-lactone. [c] *o*-Methoxyphenyl.

reaction with ynolates in excellent yield (entries 7−13). In the decarboxylation step, the conditions using 1 equiv of TsOH under reflux in toluene gave better yields. In the case of acid-sensitive products, the decarboxylation was carried out only by heating without use of an acid (entry 11). In the case of entry 13, the thiophene **21** was directly generated without heating or acid treatment. The in situ decarboxylation by base would proceed, as can be seen in the synthesis of pyrroles, which will be described next, probably due to the electron-donating thienyl substituent.

This successful result prompted us to examine the synthesis of pyrroles using α-acylaminoketones (e.g., **22**) as a substrate. Since it was sluggish at −78 °C, we carried out the reaction at −20 °C. Within 3 min, we obtained the fused β-lactone **24** in 68% yield along with the pyrrole in 15% yield. After optimization of the reaction conditions, we succeeded in obtaining the desired pyrrole in good yield in one pot at −20 °C in 3 h without treatment with acid. This result suggests a different decarboxylation pathway from that of the synthesis of furans. In situ reaction monitoring with IR spectroscopy indicated that initially the β-lactone (1821 cm^{-1}) appeared and then gradually disappeared. Also a carboxylate absorption (1678 cm^{-1}) appeared and did not decrease until quenching. These facts indicated that β-*syn*-elimination from the intermediate **23** by the LiOEt base generated in the step producing the ynolates leads to the ring opening of the β-lactone. Actually, the isolated β-lactone **24** was treated with BuLi to afford the pyrrole **26** in 75% yield. We speculate that, on quenching with water, the pyrrole was finally generated via decarboxylation and dehydration from the carboxylate **25**. This one-pot process was unsuccessful for the synthesis of furans and thiophenes due to decomposition of **6** and/or **7** at −20 °C, except for the case of **21**.

The synthesis of multisubstituted pyrroles is summarized in Table 2. Aromatic, aliphatic, and cyclic ketones (R^1 and R^2) gave the penta- and tetrasubstituted pyrroles. Sterically hindered (entries 2 and 4), electron-withdrawing (entry 3), and functionalized (entry 9) acyl groups (R^3) also provided the pyrroles. When less reactive substrates (entries 5−10) or ynolates (entry 6) were used, the reactions were carried out at 0 °C, although the electrocyclic ring opening of the β-lactone enolates should have proceeded at that temperature.[12] When the ring opening of **23** to **25** did not occur, the isolated β-lactones were decarboxylated under acidic condi-

(6) For recent examples for synthesis of multisubstituted heterocycles, see: (a) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151−2153. (b) Mathew, P.; Asokan, C. V. *Tetrahedron* **2006**, *62*, 1708−1716. (c) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468−469. (d) Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465−2468. (e) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164−11165. (f) Wang, Y.; Zhu, S. *Org. Lett.* **2003**, *5*, 745−748. (g) Mortensen, D, S.; Rodriguez, A. L.; Carlson, K. E.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2001**, *44*, 3838−3848. (h) Wills, M. S. B.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9378−9379. For reviews on furans and pyrroles, see: (i) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955−2020. (j) Balm, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238−6241. (k) Kirsch, S. *Org. Biomol. Chem.* **2006**, *4*, 2076−2080.

(7) For reviews, see: (a) Shindo, M. *Tetrahedron* **2007**, *63*, 10−36. (b) Shindo, M. *Synthesis* **2003**, 2275−2288. (c) Shindo, M. *J. Synth. Org. Chem. Jpn.* **2000**, *58*, 1155−1166. (d) Shindo, M. *Yakugaku Zasshi* **2000**, *120*, 1233−1246. (e) Shindo, M. *Chem. Soc. Rev.* **1998**, *27*, 367−374.

(8) (a) Shindo, M.; Sato, Y.; Shishido, K. *J. Am. Chem. Soc.* **1999**, *121*, 6507. (b) Shindo, M.; Sato, Y.; Shishido, K. *J. Org. Chem.* **2001**, *66*, 7818. (c) Shindo, M.; Matsumoto, K.; Sato, Y.; Shishido, K. *Org. Lett.* **2001**, *3*, 2029.

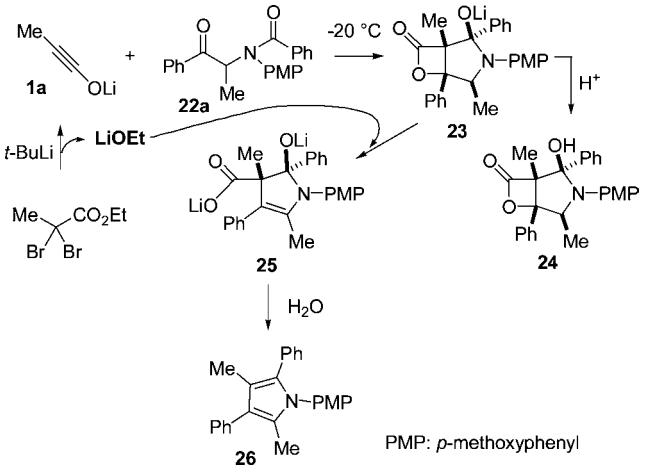
(9) Only a few examples of this category have been reported. For pyrroles, see: (a) Suzuki, M.; Miyoshi, M.; Matsumoto, K. *J. Org. Chem.* **1974**, *39*, 1980. (b) van Leusen, D.; van Echten, E.; van Leusen, A. M. *J. Org. Chem.* **1992**, *57*, 2245−2249. For thiophenes, see: (c) Liebscher, J.; Feist, K. *Synthesis* **1985**, 412−414.

(10) Shindo, M.; Yoshikawa, T.; Itou, Y.; Mori, S.; Nishii, T.; Shishido, K. *Chem.−Eur. J.* **2006**, *12*, 524−536.

(11) In the case of entry 8 (Table 1), the structure of the β-lactone intermediate was determined by X-ray crystal structure analysis. See Supporting Information.

tions to afford the pyrroles (entry 3). The fact that, in the absence of EtOLi, addition of BuLi was required (entry 11) supports the mechanism as shown in Scheme 3. As *N*-

Scheme 3

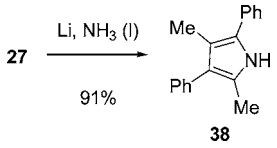


substituents (X), aryl, benzyl, and allyl groups could be used, but carbamates (X = CO_2Bn, CO_2Et) did not give the pyrroles.

The *N*-benzyl group could be removed by the Birch reduction[13] to furnish the tetrasubstituted pyrrole **38** (Scheme 4).

(12) (a) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron Lett.* **1998**, *39*, 4857−4860. (b) Shindo, M.; Sato, Y.; Shishido, K. *J. Org. Chem.* **2000**, *65*, 5443−5445. (c) Shindo, M.; Matsumoto, K.; Mori, S.; Shishido, K. *J. Am. Chem. Soc.* **2002**, *124*, 6840−6841. (d) Shindo, M.; Sato, Y.; Yoshikawa, T.; Koretsune, R.; Shishido, K. *J. Org. Chem.* **2004**, *69*, 3912−3916. (e) Mori, S.; Shindo, M. *Org. Lett.* **2004**, *6*, 3945−3948.

Scheme 4



In conclusion, we have developed a short-step synthetic method for multisubstituted furans, thiophenes, and pyrroles using ynolates. This novel [4 + 1] annulation by C2−C3 and C3−C4 bond formation should be useful for the efficient synthesis of multisubstituted heterocycles.

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Supporting Information Available: General procedures and characterization data of new compounds, synthetic method of starting materials, CIF for the β-lactone (entry 8, Table 1) (CCDC 635505), and ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0705200

(13) Pandey, P. S.; Rao, T. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 129−131.