A General Strategy for Five-Membered Heterocycle Synthesis by Cycloelimination of Alkynyl Ketones, Amides, and Thioamides

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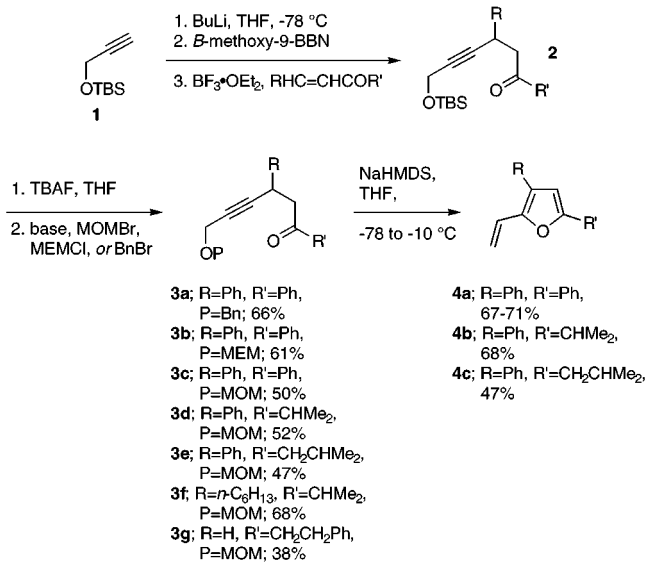
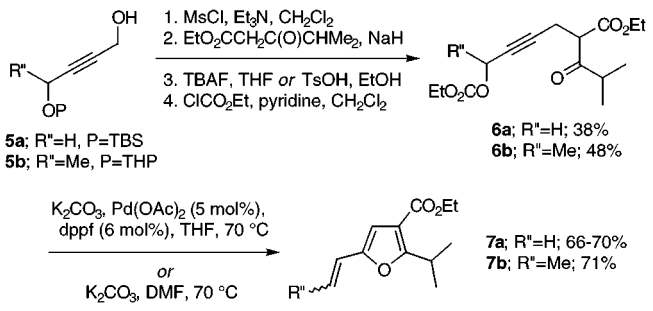
Furans are common substructures in numerous natural products, such as the cembranolides lophotoxin,[1] kallolides,[2] and pukalide.[3] These heterocycles are also found in numerous commercial products, including pharmaceuticals, fragrances, and dyes. Accordingly, many strategies have been developed for the preparation of furans.[4] Marshall and co-workers utilized 3-alkynyl allylic alcohols in S_N2' reactions to provide 2,3-disubstituted furans.[5] Another method for the formation of 2,3-disubstituted furans from the same laboratory employed Ag(I)- or Rh(I)-catalyzed cyclizations of allenyl ketones and aldehydes.[6] Palladium catalysis has also been used for the synthesis of furans. Coupling of terminal acetylenes and γ-hydroxyalkynoates followed by Pd(II)-catalyzed cyclization produced 2,4-disubstituted furans.[7] Wakabayashi et al. have used Pd(II) to promote intramolecular cyclizations of 3-alkynyl-1,2-diols to give either 2,3-disubstituted or 2,3,4-trisubstituted furans from β,γ-acetylenic ketones.[8] Numerous literature protocols for the formation of furans employ 1,3-dicarbonyl compounds. Paquette and co-workers used these starting materials to prepare a 2,3,5-trisubstituted furan as an intermediate in the total synthesis of gorgiacerone, a furanocembranolide.[9] Larock and Cacchi studied the Pd(0)-mediated cyclizations of 2-propargylic-1,3-dicarbonyl compounds,[10] and Tsuji et al. used Pd(0) catalysis for the formation of furans in the intramolecular annelation reaction of β-keto esters and either propargylic carbonates or oxiranes.[11] Other strategies based on dicarbonyl substrates use the Feist−Benary condensation of 1,2-dibromoacetate with acetoacetate to provide 2,3-disubstituted furans or the cyclocondensation of acetone dicarboxylate with 1,4-dibromobut-2-yne to give 2-vinylidenehydrofurans.[12,13] As part of our approach toward the total synthesis of lophotoxin, we were interested in a general protocol for 2-alkenylfurans. In this paper, we present the first use of unstabilized monocarbonyl systems in the formation of substituted furans. Our methodology employs alkynyl ketone enolates which undergo a thermal S_N2' O-alkylation to provide the desired heterocycles. Furthermore, we were able to extend this strategy toward novel syntheses of 1,3-oxazoles and -thiazoles.

Scheme 1



Scheme 2



The starting materials for our furan synthesis, alkynyl ketones of type **3**, were readily obtained by the BF_3•etherate-mediated Michael addition of alkynyl boranes to enones (Scheme 1).[14] Since we were interested in studying the effect of the leaving group, different protective groups (Bn, MOM, MEM) were installed at the propargylic oxygen.

Treatment of alkynyl ketones **3** with 1.1 equiv of NaHMDS at −78 °C, followed by warming to −10 °C, provided the desired alkenylfurans **4** in 47−71% yield after chromatography on SiO_2. Irrespective of the ether protective groups, substrates **3a**−**c** provided furan **4a** in 67−71% yield. However, the corresponding silyl ether **2** did not convert to furan even at elevated temperatures. Whereas aliphatic ketones with R′ = alkyl groups (e.g., **3d** and **3e**) reacted analogously to the aromatic ketones, replacement of the R substituent with alkyl groups or hydrogen led to unreactive substrates **3f** and **3g** that did not provide any furans upon exposure to NaHMDS or other bases. Even replacement of the propargylic ether substituents with better leaving groups such as benzoates and mesylates or the use of Pd(0) catalysts did not facilitate furan formation.

In contrast, cycloelimination of ketones **3** with R = H or alkyl groups was possible if an additional electron-withdrawing group was attached α to the carbonyl group (Scheme 2). β-Keto esters **6a** and **6b** were obtained by alkylation with propargylic alcohols **5a** and **5b**, respectively, and converted smoothly to furans **7a** and **7b** upon treatment with 5 mol % of $Pd(OAc)_2$ and 6 mol % of (diphenylphos-

(1) Fenical, W.; Okeeda, R. K.; Basnadurraga, M. M.; Culver, P.; Jacobs, R. S. *Science* **1981**, *212*, 1512.
(2) Look, S. A.; Burch, M. T.; Fenical, W.; Qi-tai, Z.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 5741.
(3) Missakian, M. G.; Burreson, B. J.; Scheuer, P. J. *Tetrahedron* **1975**, *31*, 2513.
(4) Eberbach, W. In *Heteroarenes I, Part 1*, 4th ed.; Kreher, R. P., Ed.; Georg Thieme Verlag: Stuttgart, 1994; Vol. E6a, pp 16−185d.
(5) Marshall, J. A.; Bennett, C. E. *J. Org. Chem.* **1994**, *59*, 6110.
(6) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1991**, *56*, 960.
(7) Trost, B. M.; McIntosh, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 7255.
(8) Wakabayashi, Y.; Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1985**, *41*, 3655.
(9) (a) Paquette, L. A.; Doherty, A. M.; Rayner, C. M. *J. Am. Chem. Soc.* **1992**, *114*, 3910. (b) Rayner, C. M.; Astles, P. C.; Paquette, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 3926.
(10) Arcadi, A.; Cacchi, S.; Larock, R. C.; Marinelli, F. *Tetrahedron Lett.* **1993**, *34*, 2813.
(11) Minami, I.; Yuhara, M.; Watanabe, H.; Tsuji, J. *J. Organomet. Chem.* **1987**, *334*, 225.
(12) Cambie, R. C.; Moratti, S. C.; Rutledge, P. S.; Woodgate, P. D. *Synth. Commun.* **1990**, *20*, 1923.
(13) Lavoisier-Gallo, T.; Rodriguez, J. *J. Org. Chem.* **1997**, *62*, 3787.
(14) Sinclair, J. A.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 1078.

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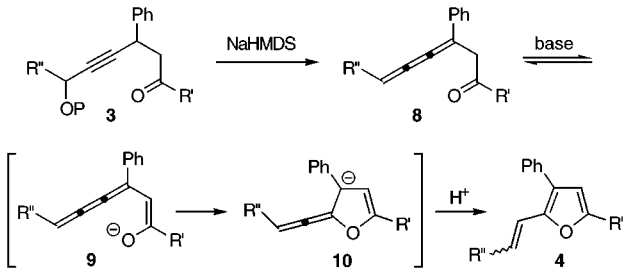
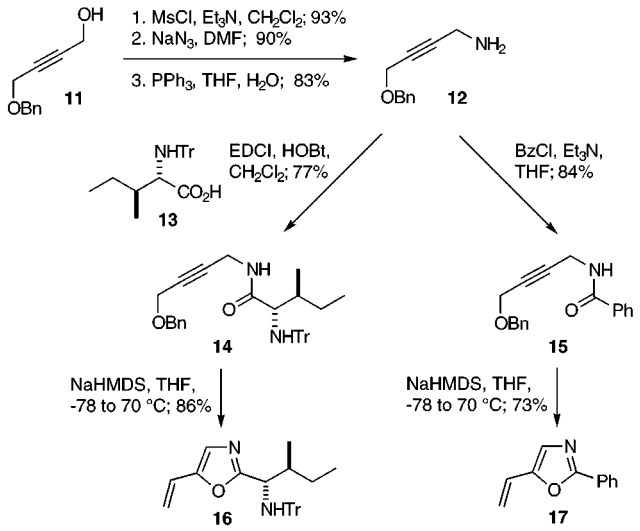
Scheme 3



Scheme 4

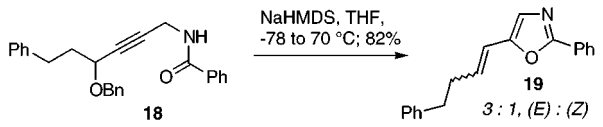


phino)ferrocene in THF or with 1 equiv of K_2CO_3 in DMF. In either case, heating to 70 °C was necessary to effect cycloelimination to the furan, and no reaction occurred with ether leaving groups in place of the carbonate.

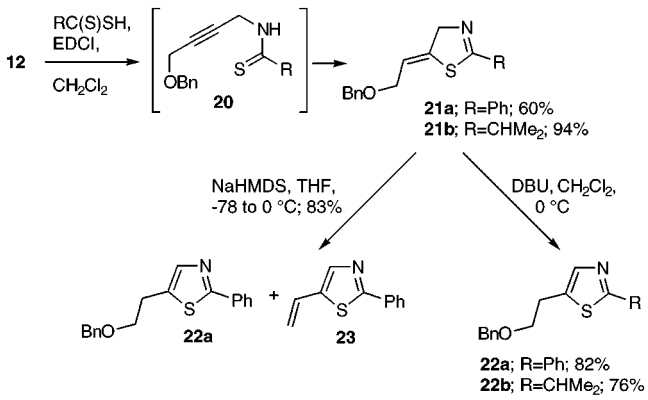
Since the presence of a phenyl substituent at the R position in ketones **3** significantly accelerates the cycloelimination to furans, we propose a mechanism for these substrates that involves cumulene **8** as a reactive intermediate (Scheme 3). Elimination of **3** to the cumulene is facilitated by the α-anion-stabilizing effect of the phenyl ring, and subsequent thermodynamically controlled enolization, cyclization, and furan formation are fast compared to the initial elimination reaction. An elimination at the preformed enolate stage leading directly to cumulene **9** is also possible. With stabilized enolates derived from *β*-keto esters **6**, a more traditional pathway involving a direct S_N2' reaction of the enolate oxygen on the propargylic leaving group provides an alternative route to alkenyl furans **7**.[13,15] Obviously, the latter pathway is also amenable to Pd(0) catalysis.

Either the mechanism invoked in Scheme 3 or a more traditional intramolecular S_N2' O-alkylation should be pertinent to the formation of other five-membered heterocycles. Accordingly, we prepared amides **14** and **15** from butynediol derivative **11** and subjected them to NaHMDS (Scheme 4). In both cases, clean oxazole formation was observed, and the desired heterocycles were obtained in good yields.[16] A single diastereomer of oxazole **16** was isolated for (*S*)-isoleucine-derived **14**, a clear indication that despite the basic conditions the cycloelimination does not readily epimerize base-labile stereocenters. As in the furan case, the preparation of more highly substituted alkenyl heterocycles is possible. A 3:1 *E*/*Z* ratio of disubstituted alkenyl oxazoles **19** was obtained from the secondary benzyl ether **18** (Scheme 5).

Scheme 5



Scheme 6



Further extension of this novel methodology to thioamide analogues of **15** provided directly the vinylthiazolines **21** after coupling of amine **12** with dithiobenzoic or dithioisobutyric acid, and none of the putative thioamide intermediates **20** were observed (Scheme 6).[17] Interestingly, as a consequence of the greater nucleophilicity of the thioamide function, spontaneous cyclization onto the triple bond had occurred. Treatment of **21a** with NaHMDS for 1 h provided a ca. 1:1 mixture of thiazole **22a** and vinylthiazole **23**, whereas the thiazoles **22a** and **22b** were obtained as the sole products in 76−82% yield after prototropic rearrangement of **21a** and **21b** in the presence of DBU.

In conclusion, we have been able to establish a novel general strategy for the preparation of five-membered heterocycles. 3-Aryl-substituted *γ*,*δ*-acetylenic ketones undergo a formal intramolecular S_N2' O-alkylation with a variety of ether-type leaving groups to provide 2,4,5-trisubstituted vinylfurans. Furthermore, these heterocycles can also be formed from the corresponding *β*-keto esters by a different mechanistic pathway that requires higher temperatures but is independent of an aryl substituent at the (propargylic) ketone *β*-carbon. In addition to furans, oxazoles and thiazoles are readily obtained under analogous reaction conditions from propargylic amides and thioamides. In the latter case, the alkynylamine-derived thioamide spontaneously cyclizes onto the triple bond under the reaction conditions of thioamide formation, and only vinylthiazoline intermediate is isolated. Subsequent alkene isomerization provides the aromatic thiazole. We are currently studying further variations of this new heterocyclic chemistry as well as its extension to imidazoles.

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Supporting Information Available: Experimental details and characterization for all new compounds. Copies of ^1H and ^{13}C NMR spectra (78 pages).

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(15) MaGee, D. I.; Leach, J. D. *Tetrahedron Lett.* **1997**, *38*, 8129.

(16) In prior work, we have observed the formation of an alkenyl oxazoline from a *π*-allylcopper complex: (a) Wipf, P.; Fritch, P. C. *J. Org. Chem.* **1994**, *59*, 4875. For the related Pd(0)-catalyzed cyclization of 1,4-disubstituted cyclopentene derivatives to give bicyclic oxazolines and other examples of amide cyclizations onto a *π*-allylpalladium complex, see: (b) Hansel, J.-G.; O'Hogan, S.; Lensky, S.; Ritter, A. R.; Miller, M. J. *Tetrahedron Lett.* **1995**, *36*, 2913. (c) Cook, G. R.; Shanker, P. S. *Tetrahedron Lett.* **1998**, *39*, 3405.

(17) Thionation of amide **15** with Lawesson's reagent led, in lower yield, to the identical vinylthiazoline, and no thioamide intermediate was observed in this reaction either.