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New Carbanionic Access to 3-Vinylindoles and 3-Vinylbenzofurans

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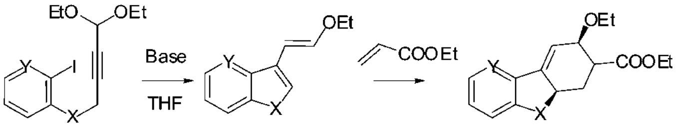
ABSTRACT



A simple route to 3-vinylbenzofurans, 3-vinylfuropyridines, and 3-vinylindoles from readily accessible acetylenic precursors is described. A standard halogen–lithium exchange triggers an irreversible addition on the triple bond, according to a 5-exo-dig heterocyclization process, followed by a lithium ethoxide elimination. A final isomerization of the exocyclic allene provides a 1,3-dienic system that can react with acrylates, in thermal or hyperbaric conditions, to provide the expected [4+2] cycloadducts.

The carbanionic ring closure is certainly one of the simplest and most direct routes to heterocycles. The vast majority of the examples studied to date take advantage of an intramolecular nucleophilic addition of organometallic compounds onto a terminal ethylenic moiety.[1] Acetylenic substrates have been much less considered, except by Johnson[2] who opened a route to benzofurans, indoles, and benzothiophenes through a 5-endo-dig process as early as 1986. Actually, the addition of alkyllithium compounds onto acetylenes has seldom been described,[3] even for carbocyclizations. Early results were reported by Kandill,[4a] Ward,[4b] and particularly Negishi,[5] who prepared cyclopentanes and indanes through a 5-exo-dig route.

Recently, this field has been investigated more, mainly by Bailey and co-workers[6] who found that intramolecular alkyllithium additions on triple bonds give handy access to functionalized carbocycles, with a ring size from 4 to 6. In three cases, cascade reactions have also been reported, which implies either a re-addition of an intermediate vinyllithium[7] or an elimination of a lithium alkoxide[6b,8] (Figure 1).

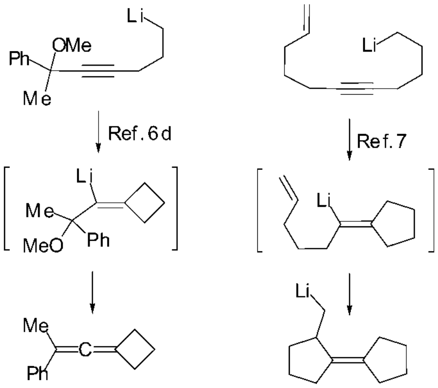


Figure 1. Anionic cyclization of lithioacetylenic compounds.

Our interest in the conjugated elimination reactions involving acetals[9] and propargylic systems[9c] led us to examine possible extensions of these results to new heterocyclization processes. We first considered propargylic acetal

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[1] Inter alia: (a) Lorthiois, E.; Marek, I.; Meyer, C.; Normant, J.-F. *Tetrahedron Lett.* **1995**, *36*, 1263−1266. (b) Bailey, W. F.; Punzalan, E. R. *Tetrahedron Lett.* **1996**, *37*, 5435−5436. (c) Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1996**, *61*, 2594−2595. Enantioselective versions: (d) Bailey, W. F.; Mealy, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 6787−6788. (e) Sanz Gil, G.; Groth, U. M. *J. Am. Chem. Soc.* **2000**, *122*, 6789−6790. (f) Ashweek, N. J.; Coldham, I.; Snowden, D. J.; Vennall, G. P. *Chem. Eur. J.* **2002**, *8*, 195−207.

[2] Johnson, F.; Subramanian, R. *J. Org. Chem.* **1986**, *51*, 5041−5043.

[3] Normant, J.-F.; Alexakis, A. *Synthesis* **1981**, 841−870.

[4] (a) Kandil, S. A.; Dessy, R. E. *J. Am. Chem. Soc.* **1966**, *88*, 3027−3034. (b) Ward, H. R. *J. Am. Chem. Soc.* **1967**, *89*, 5517−5518.

[5] Wu, G.; Cederbaum, F. E.; Negishi, E. *Tetrahedron Lett.* **1990**, *31*, 493−496.

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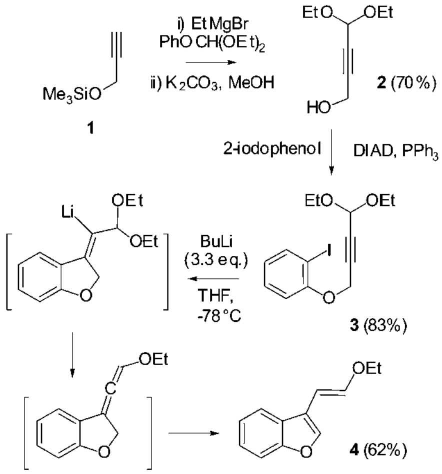
2, readily prepared[9c] from propargyloxytrimethylsilane **1** (Scheme 1). A Mitsunobu condensation with 2-iodophenol provided aryl ether **3** in good yield. Next, the iodine−lithium exchange performed with an excess of *n*-BuLi in classical conditions took place selectively despite the acidic propargylic position. An anionic cascade then ensued, started by a 5-exo-dig addition of the aryllithium on the triple bond. The vinyllithium intermediate evolves with loss of lithium ethoxide. The putative exocyclic allene rearranged in this basic medium to 3-vinylbenzofurane **4**, recovered in 62% yield and as a pure (*E*) isomer.[10]

Scheme 1. Anionic Access to Vinylbenzofurans

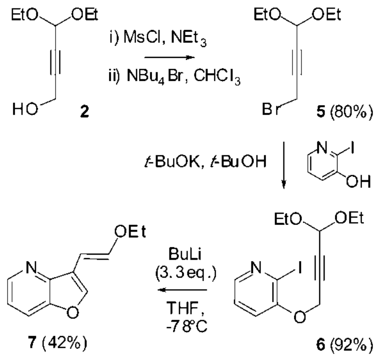


Interestingly, the preliminary isomerization of the triple bond of **3** into the corresponding allene followed by the iodine−lithium exchange led to the same product **4** in higher yield (85%) but as a (*E*)/(*Z*) mixture (86:14).

The efficiency of this heterocyclization is probably due to the irreversible character of the elimination of a lithium ethoxide that prevents the reopening of the benzofuran skeleton at the vinyllithium stage. This was checked by (i) performing the same reaction in diethyl ether, a solvent in which the β-elimination hardly takes place.[9c] Compound **4** is then obtained in low yield (18%), (ii) replacing the acetal group with a methyl group (replacing **2** in Scheme 1 by but-2-yn-1-ol), which impedes the cyclization, a partial isomerization of the triple bond into the corresponding allene being observed in this case.

The same sequence of reactions was also applied to iodopyridine **6**, prepared from **2** as described in Scheme 2.

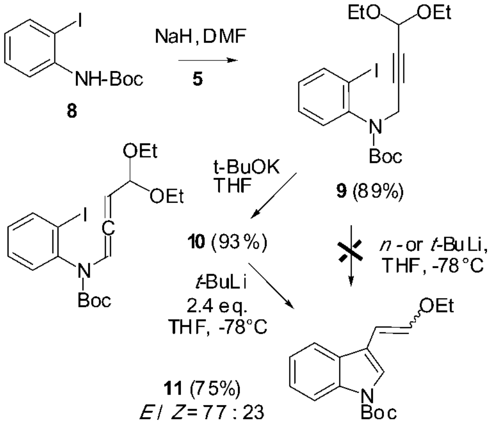
Scheme 2. Anionic Access to Vinylfuro[3,2-*b*]pyridine



The halogen−metal exchange gave access to 3-vinylfuro[3,2-*b*]pyridine **7** in modest yield but with total (*E*) selectivity.

We then tried to apply a comparable sequence to the construction of the indolic skeleton. This was achieved in 3 steps from *N*-Boc-2-iodoaniline **8**, as depicted in Scheme 3.

Scheme 3. Anionic Access to Vinylindole



The alkylation of **8** by the propargylic bromide **5** gives precursor **9** in good yield. Neither the *n*- nor the *t*-BuLi-induced iodine−lithium exchange works properly in this case and a complex mixture of compounds was obtained. However, by first isomerizing the triple bond into allene **10** (using *t*-BuOK in THF) the desired ring-closure could be effected by the action of 2.4 equiv of *t*-BuLi. The indole nucleus was thus obtained in 75% yield and as a 77:23 mixture of the *E* and *Z* isomers.

These 3-vinyl heterocycles are fine building blocks, particularly for alkaloid synthesis, because of their dienic moiety that can be engaged in Diels−Alder cycloadditions.[11] We thus reacted **4**, **7**, and **11** with ethyl acrylate under thermal and hyperbaric conditions. This dienophile indeed

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(6) Inter alia: (a) Bailey, W. F.; Ovaska, T. V.; Leipert, T. K. *Tetrahedron Lett.* **1989**, *30*, 3901−3904. (b) Bailey, W. F.; Ovaska, T. V. *Tetrahedron Lett.* **1990**, *31*, 627−630. (c) Bailey, W. F.; Ovaska, T. V. *J. Am. Chem. Soc.* **1993**, *115*, 3080−3090. (d) Bailey, W. F.; Aspris, P. H. *J. Org. Chem.* **1995**, *60*, 754−757. (e) Bailey, W. F.; Wachter-Jurcsak, N. M.; Pineau, M. R.; Ovaska, T. V.; Warren, R. R.; Lewis, C. E. *J. Org. Chem.* **1996**, *61*, 8216−8228.

(7) Bailey, W. F.; Ovaska, T. V. *Chem. Lett.* **1993**, 819−820.

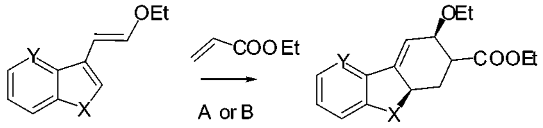
(8) Krief, A.; Remacle, B.; Mercier, J. *Synlett* **2000**, 1443−1446.

(9) (a) Guillam, A.; Toupet, L.; Maddaluno, J. *J. Org. Chem.* **1998**, *63*, 5110−5122. (b) Guillam, A.; Toupet, L.; Maddaluno, J. *J. Org. Chem.* **1999**, *64*, 9348−9357. (c) Le Strat, F.; Maddaluno, J. *Tetrahedron Lett.* **2000**, *41*, 5367−5371.

(10) A related intermediate lithiated benzofurane has been recently proposed: Barluenga, J.; Fañanás, F. J.; Sanz, R.; Marcos, C. *Org. Lett.* **2002**, *4*, 2225−2228.

appeared to be a good probe for the reactivity and regiodirectivity imposed by such 1,2,4-trisubstituted systems (Scheme 4).

Scheme 4. Cycloadditions with 3-Vinyl Heterocycles



4: X = O, Y = CH
7: X = O, Y = N
11: X = N-Boc, Y = CH

12: X = O, Y = CH
13: X = O, Y = N
14: X = N-Boc, Y = CH

The results presented in Table 1 indicate that, despite their aromatic character, these dienes provide the expected tricyclic adducts in fair to good yields and with moderate endo/exo selectivities. Selectivity was strongly influenced by the activation mode. While the exo isomer is preferred at reflux in toluene, its endo epimer becomes the major product under high pressure.[12] Worthy of note are the regioselectivity, fully controlled by the ethoxy group, and the absence of rearomatization of the heterocycle in **12**−**14**.

Table 1. Reaction of Dienes **4**, **7**, and **11** with Ethyl Acrylate

entry	diene	conditions[a]	*t* (h)	yield (%)	*endo*/*exo*
1	**4**	A	72	59	37:63
2	**4**	B	18	53	72:28
3	**7**	A	148	65	32:68
4	**7**	B	48	72	72:28
5	**11**	A	18	61[b]	27:73
6	**11**	B	36	70[b]	70:30

[a] Conditions: (A) Tol, 110 °C, 1 atm; (B) THF, room temperature, 12 kbar. [b] Yields based on **11** (*E*)-isomer. (*Z*)-**11** was recovered unaltered.

In conclusion, we describe a simple route to 3-vinyl heterocycles from readily available acetylenic precursors. Standard halogen−lithium exchange conditions trigger, *in the absence of any transition or heavy metal*, an irreversible anionic cascade based on a 5-exo-dig heterocyclization that ends up providing 3-vinylbenzofuran, furo[3,2-*b*]pyridine, and indole nuclei. These dienes can then be used in [4+2] cycloadditions in thermal or hyperbaric conditions. Details about the scope of these reactions and their extension to 6-exo-dig processes will be published in due time.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026351V

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[11] See for instance: (a) Saroja, B.; Srinivasan, P. C. *Synthesis* **1986**, 748−749. (b) Eberle, M. K.; Shapiro, M. J.; Stucki, R. *J. Org. Chem.* **1987**, *52*, 4661−4665. (c) Pindur, U. *Heterocycles* **1988**, *27*, 1253−1268. (d) Kraus, G. A.; Thomas, P. J.; Bougie, D.; Chen, L. *J. Org. Chem.* **1990**, *55*, 1624−1627. (e) Pearson, J. R.; Porter, Q. N. *Aust. J. Chem.* **1991**, *44*, 1085−1095. (f) Sundberg, R. J. *Indoles*; Academic Press: London, UK, 1996. (g) Kinsman, A. C.; Kerr, M. A. *Org. Lett.* **2001**, *3*, 3189−3191.

[12] Jenner, G. *Tetrahedron* **1997**, *53*, 2669−2695.