Pergamon

Tetrahedron Letters, Vol. 36, No. 3, pp. 343-346, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(94)02265-8

A $^{-}CH_2CH{:}C^{+}NR_2$ Synthon: Novel Preparations of 1,3-Disubstituted Allylamines and of 1,2-Diaryl Pyrroles.

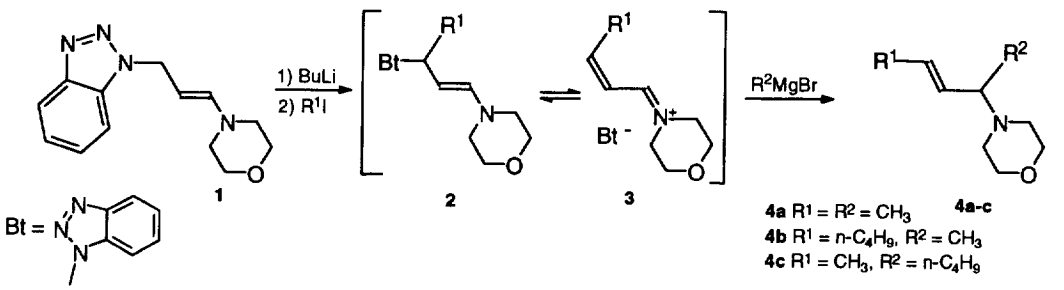
Alan R. Katritzky,* He-Xi Chang and Sergei V. Verin

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200, U.S.A.

Abstract: 1-(3-Morpholinoprop-2-enyl)benzotriazole (**1**) is a useful synthon of the type [$^{-}CH_2$-CH=$C^{+}NR_2$] as demonstrated by the preparation of allylamines **4**. It can also provide a [$^{+}$ $^{-}$CH-CH=CH^{+}] fragment for the synthesis of 1,2-diarylpyrroles **6**.

We have recently demonstrated the considerable synthetic utility of benzotriazole derivatives.[1] We now introduce 1-(3-morpholinoprop-2-enyl)benzotriazole (**1**) as a valuable synthetic precursor of allylamines of type **4** and 1,2-diarylpyrroles **6**.

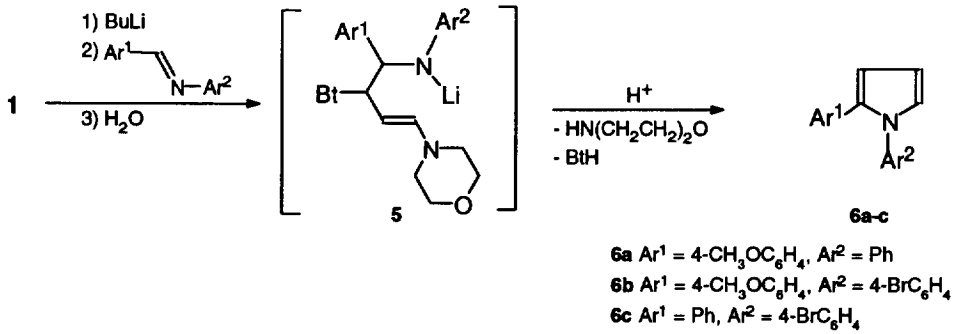
The utility of compound **1** is based on the ability of its α-lithio derivative to react regiospecifically with various electrophiles to yield products containing a labile benzotriazole moiety. Such intermediates can be further functionalized in a number of ways. Thus, treatment of **1** with butyl lithium, followed by the addition of iodoalkanes, results in the formation of derivatives **2**. By analogy with other benzotriazole derivatives, intermediates **2** presumably exist in equilibrium with ion pairs **3**.[2] Subsequent addition of Grignard reagents to the reaction mixture gives allylamines **4a-c**[3] in 64-73% yields (Scheme 1). This reaction is related to previous preparations of allylamines by the addition of suitable nucleophiles to α,β-unsaturated imines and iminium salts.[4-10] However, our method is the first to enable the construction of specific allylamines in a one pot process *via* successive attachments of two different radicals to the three carbon unit.



Scheme 1

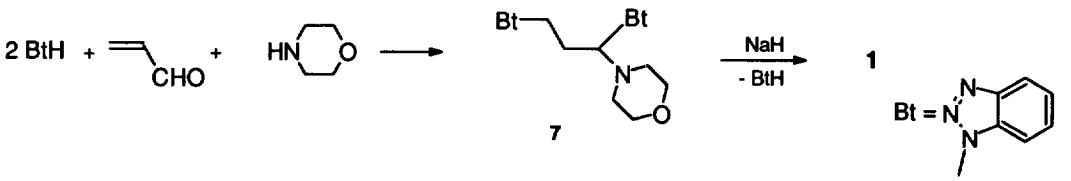
Treatment of **1** with butyl lithium, followed by the addition of diarylimines presumably yields diamines **5**, which undergo cyclization *in situ* to give 1,2-diarylpyrroles **6a-c** in 60-68% total yields[11] on brief heating in the presence of a catalytic amount of sulfuric acid (Scheme 2). This method, along with that recently reported[12] using 1-propargylbenzotriazole as a C_3-fragment, may be classified as [3+2]-pyrrole syntheses as both methods involve formation of the *a,d* bonds. Both compound **1** and 1-propargylbenzotriazole provide three-carbon fragments with one nucleophilic and one electrophilic terminus, while all previously reported pyrrole syntheses of this type utilize a C_3-building block with two electrophilic termini.[13]

To date, only two 1,2-diarylpyrroles with the 3,4,5-positions unsubstituted have been reported, although they appear to possess important neuroleptic activity.[14,15] 1,2-Diphenylpyrrole was previously obtained in 57% yield from aniline and β-benzoylacetaldehyde,[15] the latter reagent prepared in 47% overall yield in a three step procedure. Alternatively, condensation of N-(α-cyanobenzyl)aniline and its *o*-chloro analog with acrolein gave 1,2-diphenylpyrrole[16] and 1-phenyl-2-(*o*-chlorophenyl)pyrrole[17] in 27% and 31% yields, respectively.



Scheme 2

Starting material **1** is readily prepared in quantity by a two step procedure.[18] Reaction of acrolein with two equivalents of benzotriazole and one equivalent of morpholine in refluxing toluene forms adduct **7**, which eliminates one benzotriazole moiety on treatment with sodium hydride (Scheme 3).



Scheme 3

The synthetic applications of compound **1** illustrate the advantages of benzotriazole as a synthetic auxiliary (for a review see [1]). Thus, benzotriazole can either be displaced by Grignard reagents (as in the preparation of allylamines **4**) or other nucleophiles, or eliminated in basic (preparation of **1** from **7**) or acidic (preparation of pyrroles **6**) conditions. Significantly, benzotriazole can reverse polarity *via* the formation of adducts; the β-carbon of acrolein is strongly electrophilic, whereas in the anion of **1** it is the nucleophilic center. In conclusion, 1-(3-morpholinoprop-2-enyl)benzotriazole (**1**) is a useful synthon of the type [$^{-}CH_2$-CH=$C^{+}NR_2$] or [$^{+}$ $^{-}$CH-CH=CH^{+}]. Although in this work NR_2 was uniformly morpholino, the procedure is probably of general application to other dialkylamino groups.

REFERENCES AND NOTES

1. Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683-2732.
2. Katritzky, A. R.; Yannakopoulou, K. *Heterocycles* **1989**, *28*, 1121-1134.
3. *Preparation of allylamines **4a-c***. To a solution of 1.7g (7 mmoles) of **1** in 65 ml of THF at -78 °C under nitrogen, a solution of n-BuLi (7.3 mmoles) in cyclohexane was added dropwise. The mixture was stirred for 15 min and iodoalkane (7.6 mmoles) was added. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. A freshly prepared solution of Grignard reagent (7.6 mmoles) in ether was added and the mixture stirred at room temperature for 12 h. The solution was hydrolyzed with saturated ammonium chloride, extracted with ether and the organic layer washed with a 2N solution of NaOH until no benzotriazole was detected. The solution was dried with $MgSO_4$, the solvent evaporated and the residue purified by vacuum distillation.
   All compounds **4a-c** were characterized by ^{1}H and ^{13}C NMR spectra, as well as elemental analysis. For example **4b**; ^{1}H NMR ($CDCl_3$): δ 0.89 (t, 3H, CH_3, J = 7.1 Hz), 1.14 (d, 3H, CH_3, J = 6.6 Hz), 1.35 (m, 4H, -CH_2-CH_2-), 2.03 (m, 2H, -CH_2-CH=), 2.50 (m, 4H, morpholine), 2.80 (m, 1H, -CH-N), 3.70 (t, 4H, morpholine, J = 4.7 Hz), 5.35 (dd, 1H, vinyl, J = 12.0, 8.0 Hz), 5.50 (dt, 1H, vinyl, J = 12.0, 9.8 Hz); ^{13}C NMR ($CDCl_3$): δ 13.82, 17.88, 22.10, 31.40, 31.92, 50.45, 62.75, 67.12, 131.51, 132.46.
4. Walter, M.; Besendorf, H.; Schnider, O. *Helv. Chim. Acta.* **1961**, *44*, 1546-1554.
5. Gupton, J. T.; Colon, C. *Synth. Commun.* **1984**, *14*, 271-279.
6. Gawley, R. E.; Chemburkar, S. *Tetrahedron Lett.* **1986**, *27*, 2071-2074.
7. Tubéry, F.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1987**, *28*, 6457-6460.
8. El-Jazouli, M.; Masson, S.; Thuillier, A. *Bull. Soc. Chim. Fr.* **1988**, 875-882.
9. Hua, D. H.; Bensoussan, D.; Bravo, A. A. *J. Org. Chem.* **1989**, *54*, 5399-5402.
10. Nakagawa, M.; Kawate, T.; Yamazaki, H.; Hino, T. *J. Chem. Soc. Chem. Commun.* , **1990**, 991-992.

11. *Preparation of diarylpyrroles* ***6a-c***. To a solution of 0.74g (3 mmoles) of **1** in 15 ml of THF at -78 °C under nitrogen, a solution of n-BuLi (3.1 mmoles) in cyclohexane was added dropwise. The mixture was stirred for 15 min and a solution of corresponding imine (3.3 mmoles) in 10 ml of THF was added dropwise. The mixture was stirred for 30 min, then 2.5 ml of water followed by 2.5 ml of acetic acid were added. The mixture was allowed to warm to room temperature and was then refluxed for 10 min, cooled and 1 ml of sulfuric acid was added. The mixture was again refluxed for 4 min. The mixture was poured into 40 ml of water, extracted with 30 ml of ethylacetate and the organic layer washed with 50 ml of a 5% solution of sodium carbonate. The solvent was evaporated and the residue purified by column chromatography (silica gel - chloroform/hexane 1:1).
All compounds **6a-c** were characterized by ^{1}H and ^{13}C NMR spectra, as well as elemental analysis. For example **6c**; ^{1}H NMR ($CDCl_3$): δ 6.36 (dd, 1H, 4-H, $J_{4,3}$= 3.5, $J_{5,4}$= 2.8 Hz), 6.43 (dd, 1H, 3-H, $J_{4,3}$= 3.5, $J_{5,3}$= 1.8 Hz), 6.89 (dd, 1H, 5-H, $J_{5,4}$= 2.8, $J_{5,3}$= 1.8 Hz), 7.01-7.05 (m, 2H, phenyl), 7.10-7.13 (m, 2H, phenyl), 7.17-7.25 (m, 3H, phenyl), 7.40-7.43 (m, 2H, phenyl); ^{13}C NMR ($CDCl_3$): δ 109.70, 111.12, 120.10, 124.11, 126.52, 127.11, 128.20, 128.35, 132.12, 132.65, 133.80, 139.57.
12. Katritzky, A. R.; Li, J.; Gordeev, M. F. *Synthesis* **1994**, 93-96.
13. Sundberg, R. I. "Constraction of pyrrole ring by processes involving formation of two bonds" In *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R.; Rees, C. W. Eds Pergamon Press: New York, **1984**, 4, 328-343.
14. van Wijngaarden, I.; Kruse, C. G.; van der Heyden, J. A. M.; Tulp, M. Th. M. *J. Med. Chem.* **1988**, *31*, 1934-1940.
15. Kruse, C. G.; Bouw, J. P.; van Hes, R.; Kuilen, A.; Hartog, J. A. J. *Heterocycles* **1987**, *26*, 3141-3151.
16. Treibs, A.; Derra, R. *Liebigs Ann. Chem.* **1954**, *589*, 176-187.
17. Grimshaw, J.; Hewitt, S. A. *J. Chem. Soc. Perkin Trans. 1* **1990**, 2995-2998.
18. *Preparation of* ***1***. A mixture of 120g (1 mole) of benzotriazole, 37 ml of acrolein [90% reagent (0.5 mole)] and 300 ml of toluene was refluxed for 5 min, cooled to 40 °C and 45 ml (0.5 mole) of morpholine was added. The mixture was refluxed for 45 min, cooled and 500 ml of hexane was added. The liquid phase was decanted from the oil, which was heated to boiling with 500 ml of ether several times until it became a white solid (**7**), 114g (73%), m.p. 125-127 °C. A suspension of 28g (0.07 mole) of **7** and 3.6g (0.15 mole) of sodium hydride in 70 ml of THF was heated carefully to boiling, refluxed for 4 h and left overnight at room temperature. The reaction mixture was poured onto 150g of ice and the crystalline product filtered and air dried to yield 12.3g (64%) of **1** in a pure state, m.p. 110-112 °C.

(*Received in USA* 31 *August* 1994; *revised* 9 *November* 1994; *accepted* 15 *November* 1994)