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Enehydroxylamines as Versatile Compounds in 3,3-Sigmatropic Rearrangements†

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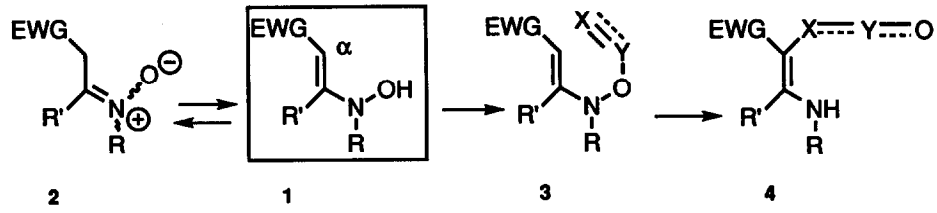
Abstract: Enehydroxylamines react readily, in the presence of base, with electrophiles containing unsaturation to afford intermediates that, either spontaneously or upon heating, lead *via* a 3,3-sigmatropic rearrangement to α-substituted products.

Enehydroxylamines **1**, tautomers of the nitrones **2**, are compounds with an interesting chemistry, owing to the presence in the same molecule of an enaminic nitrogen and a weak N-O bond. These compounds have been frequently postulated as intermediates in reactions of certain nitrones with acyl chlorides but seldom isolated. [1,2]



2 **1** **3** **4**

EWG = electron - withdrawing group

Scheme 1

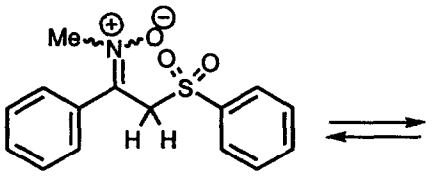
We report in this communication[3] results of our study of representatives of **1** (Scheme 1) with a variety of electrophiles, where facile α-substitution, as depicted in **4**, was observed, most probably through a 3,3-sigmatropic rearrangement of the initially formed unstable intermediate **3**. Compounds **5a** and **5b** (Scheme 2) could be easily prepared by reaction of N-methyl hydroxylamine with the appropriate cyclic 1,3-diketone in toluene at room temperature.[4,5] Reaction of **5a** with cyanogen bromide (1 eq. or 3 eq.) in the presence of DABCO, in THF, at room temperature (4 h) yielded only **6a** in 68% yield (Scheme 2, equation 1). Similarly **5b** led to **6b** (83%). However with the more powerful electrophile, 1-cyano-4-N,N-dimethylaminopyridinium

† *This paper is dedicated with admiration to Professor Sir Derek Barton on the occasion of his 75th birthday.*

bromide [6] (CAP) (3 eq.), and N,N-diisopropyl-N-ethylamine as the base, the *cyano* compounds **7a** or **7b** were obtained (equation 2). Other electrophiles such as PhCOCl (equation 3), $MeSO_2Cl$ (equation 4) and N,N-dimethylthiocarbamoyl chloride (equation 5), reacted smoothly with **5a** or **5b**, in the presence of base, and afforded products **8** (**a**,**b**), **9** (**a**,**b**) and **10** (**a**, **b**) respectively in good to excellent yields. The carbinolamines **11a** and **11b**, obtained from **5a** and **5b**, respectively, with methyl propiolate, were smoothly dehydrated (toluene, Δ) to yield the synthetically useful pyrrole derivatives **12a** [7] and **12b** (equation 6). With phenyl isocyanate (2.5 eq.) **5a** yielded **13a** (equation 7) through a sequence of reactions involving the formation of a carbamate derivative, followed by rearrangement, decarboxylation of the resulting N-phenyl carbamic acid and subsequent reaction of the product formed with a second equivalent of the electrophile.

Simple open chain nitrones, such as the one derived from acetophenone and N-methyl hydroxylamine failed to give any useful products. However, the nitrone **14**, while yielding the bromo compound **16** (69%) with BrCN [8] and base, generated the expected imidazolone derivative **17** in 80% yield *via* **15**, when treated successively with Hunig's base and CAP.

In conclusion, it is shown that cyclic enehydroxylamines are useful in 3,3-sigmatropic reactions, whereby a sulphur, an oxygen, a nitrogen and a carbon atom can be selectively introduced at the α-position by the appropriate choice of reagents, under mild conditions, to provide cyclohexane molecules with three contiguous but different functional groups.



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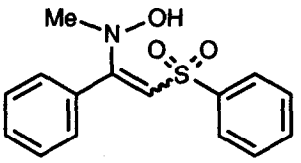

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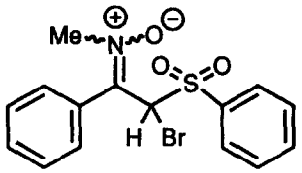

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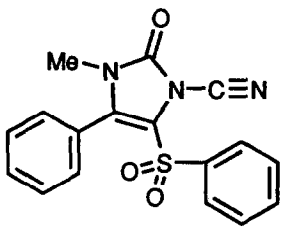

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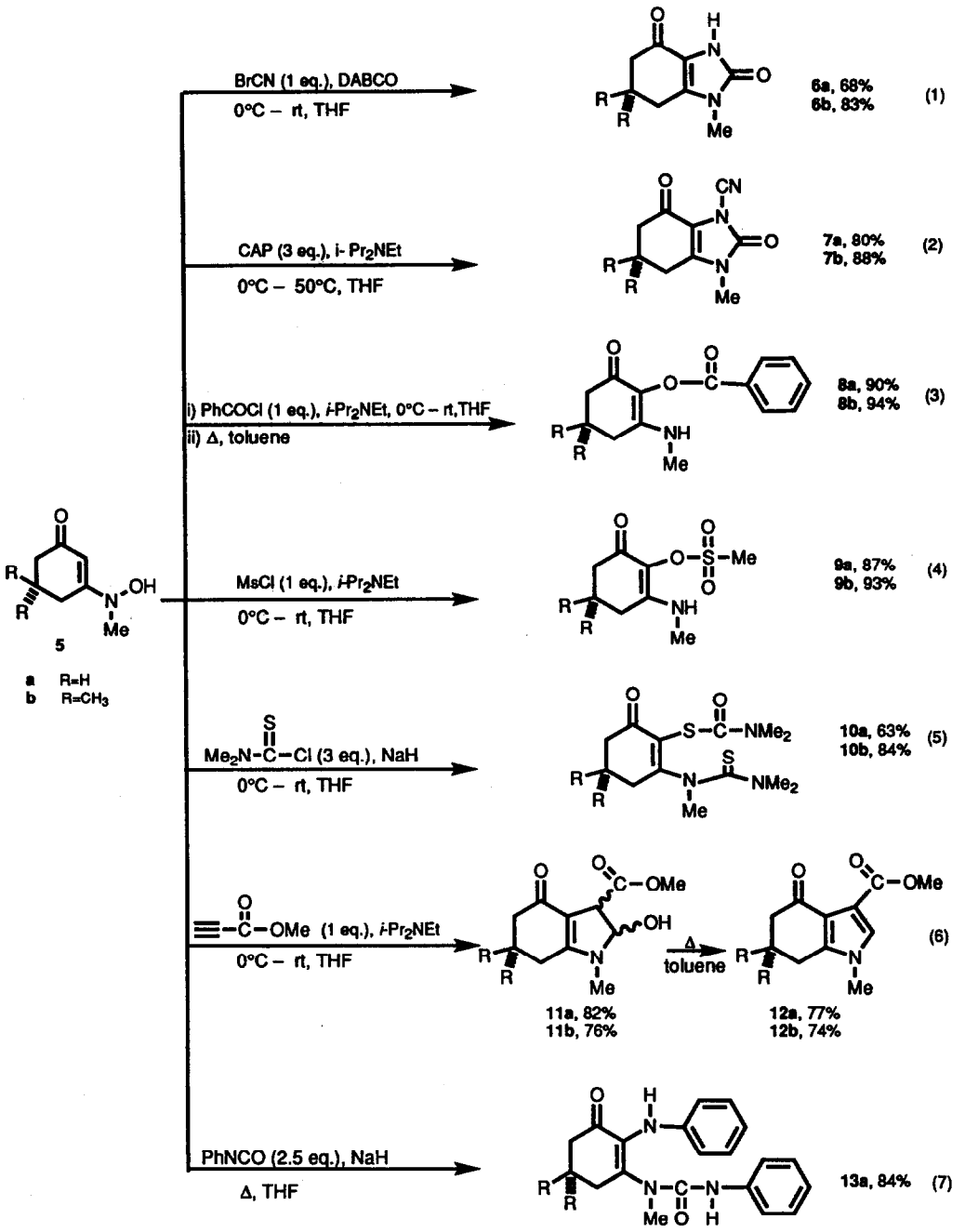
BrCN (1 eq.), DABCO
0°C – rt, THF
6a, 68%
6b, 83%
(1)
CAP (3 eq.), i- Pr2NEt
0°C – 50°C, THF
7a, 80%
7b, 88%
(2)
i) PhCOCl (1 eq.), i-Pr2NEt, 0°C – rt,THF
ii) Δ, toluene
8a, 90%
8b, 94%
(3)
MsCl (1 eq.), i-Pr2NEt
0°C – rt, THF
9a, 87%
9b, 93%
(4)
Me2N-C(=S)-Cl (3 eq.), NaH
0°C – rt, THF
10a, 63%
10b, 84%
(5)
HC≡C-C(=O)-OMe (1 eq.), i-Pr2NEt
0°C – rt, THF
11a, 82%
11b, 76%
Δ
toluene
12a, 77%
12b, 74%
(6)
PhNCO (2.5 eq.), NaH
Δ, THF
13a, 84%
(7)
5
a R=H
b R=CH3

Scheme 2

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2. Blechert, S. *Synthesis*, **1989**, 71-82.

3. This work was presented in part at the VIIth FECHEM Conference on Heterocycles in Bio-organic Chemistry, Santiago de Compostela (Spain), 26-29th September, 1993.

4. A mixture of N-methyl hydroxylamine HCl (0.036 eq.) and Et_3N (0.036 eq.) in Na-dried toluene, after being stirred vigorously under N_2 at room temperature, was filtered and the filtrate treated dropwise with a toluene solution of 1,3-cyclohexanedione (0.024 eq.). After 1,5 h the solvent was removed *in vacuo* and the residue crystallised to yield pure **5a** (59%): m.p. 126-128 °C (EtOAc-MeOH); selected NMR data δ ($CDCl_3$) 3.350 (3H, s, Me), 5.460 (1H, s, H-2, D_2O exchange), 7.617 (1H, br s, D_2O exchange); m/z (%) 141 [M^+] (85), 125 [M^+-16] (26), 113 (100). **5b** : m.p. 158-160 °C ($CHCl_3$-n-hexane) (lit.[5] m.p. 158-160 °C).
6a : m.p. 241-242 °C (dec.) (Et_2O-CH_2Cl_2); **6b** : m.p. 236-238 °C (dec.) (Et_2O-CH_2Cl_2); **7a** : m.p. 204-205 °C (EtOAc); **7b** : m.p. 184-185 °C (CH_2Cl_2-EtOAc); **8a** and **8b** oils; **9a** : m.p. 147-148 °C (Et_2O-CH_2Cl_2); **9b** : m.p. 141-142 °C (Et_2O-CH_2Cl_2); **10a** : m.p. 133-134 °C (Et_2O-CH_2Cl_2); **10b** : m.p. 125-126 °C (Et_2O-CH_2Cl_2); **11a** : oil; **11b** : m.p. 147-149 °C (dec.) (Et_2O-CH_2Cl_2); **12a** : m.p. 167-168 °C (Et_2O-CH_2Cl_2); **12b** : m.p. 142-143 °C (Et_2O-CH_2Cl_2); **13a** : m.p. 225-228 °C (dec.) (EtOAc-MeOH); **14** : m.p. 139-141 °C (Et_2O-CH_2Cl_2); **16** : m.p. 130-131 °C (Et_2O-CH_2Cl_2); **17** : m.p. 177-178 °C (EtOH).
All new compounds showed satisfactory spectroscopic data together with microanalysis and/or mass spectrometry data.

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7. Compounds of this type have been extensively used for the synthesis of 4-substituted indole derivatives: Matsumoto, M.; Watanabe, N. *Heterocycles*, **1984**, *22*, 2313-2316; Hatanaka, N.; Matsumoto, M. *Heterocycles*, **1986**, *24*, 1963-1971; Hatanaka, N.; Watanabe, N.; Matsumoto, M. *Heterocycles*, **1986**, *24*, 1987-1996, and references therein.

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