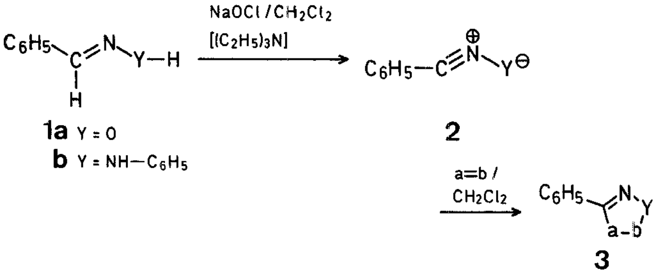
A Simplified Synthesis of Unsaturated Nitrogen-Heterocycles using Nitrile Betaines

George A. Lee

Dow Chemical USA, Central Research, New England Laboratory, P.O. Box 400, Wayland, Massachusetts 01778, U.S.A.

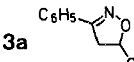
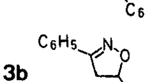
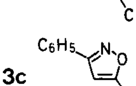
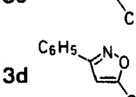
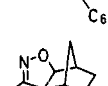
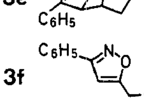
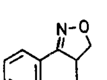
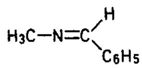
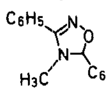
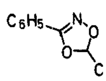
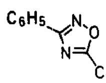
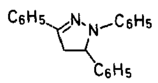
Nitrile ylids have received extensive study and synthetic use as reactive intermediates leading to heterocyclic systems[1,2]. The nitrile ylids may also be functionalized with a group capable of serving as an internal dipolarophile to allow the preparation of fused-ring heterocycles[3]. Typically, reactive nitrile oxides are generated by oxidative dehydrogenation of aldoximes or by dehydration of primary nitro compounds. In 1968, Grundmann et al.[4] described a mild and efficient procedure for generating nitrile oxides by reacting aldoximes first with *N*-bromosuccinimide (NBS) in dimethylformamide followed by treatment with sodium methoxide or triethylamine. The resulting nitrile oxides were then recovered in good yield and subsequently reacted with various dipolarophiles to afford heterocyclic products.

As an outgrowth of our previous work with phase transfer catalyzed (PTC) hypochlorite oxidation of alcohols and amines[5], we have attempted a similar dehydrochlorination of oximes or hydrazones of aldehydes to generate these reactive nitrile betaines[6]. This report describes a very simple and efficient interfacial process for the generation of a variety of nitrile betaines **2** from **1a** or **1b** *in situ* and their simultaneous trapping with dipolarophiles (a = b) to produce in many cases, excellent yields of heterocyclic derivatives **3**. Thus, our method provides a convenient, high yield, one-pot procedure for forming desired heterocyclic products.



Typically, the oxime **1a** or hydrazone **1b** is added dropwise over 15 min to a mixture of an inert, water-immiscible organic solvent containing an equivalent amount of the dipolarophile and a catalytic quantity of an organic base (triethylamine)[7], and an aqueous sodium hypochlorite[8] solution. After the reaction is complete (from 30 min to 2 h), the layers are separated and the product **3** is isolated. The Table provides a survey of

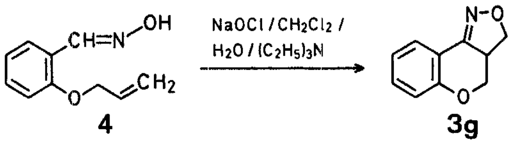
Table. Cycloaddition of *in situ* Generated Nitrile Ylids with Reactive Dipolarophiles

Reactants		Product		Yield	m.p. [°C] or b.p. [°C]/torr	
1	Dipolarophile			[%][a]	found	reported
1a	$C_6H_5-CH=CH_2$	**3a**		93[b]	73–75°	76°[12]
1a	$n\text{-}C_4H_9-CH=CH_2$	**3b**		89[c]	39–40.5°	41°[13]
1a	$n\text{-}C_4H_9-C\equiv CH$	**3c**		54[c]	131°/ 0.25	148°/ 0.6[13]
1a	$C_6H_5-C\equiv CH$	**3d**		>50[c]	141–142°	141°[13]
1a		**3e**		70[c]	99–100°	99– 100°[14]
1a	$HC\equiv CH-CH_2-Cl$	**3f**		58[c]	69–70°	69.5°[13]
4		**3g**		90[b]	62–63°	62°[10]
1a	 $H_3C-N=C(H)C_6H_5$	**3h**		95[b]	105–106°	105°[1]
1a	$C_6H_5-CH=O$	**3i**		83[b,d]	40–42°	41– 42°[15]
1a	$C_6H_5-C\equiv N$	**3j**		19[b]	107– 108.5°	106– 107°[11]
1b	$C_6H_5-CH=CH_2$	**3k**		46[b,e]	134– 135°	136– 137.5°[16]

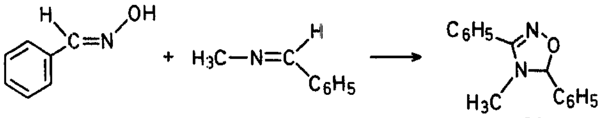
[a] Yields of product isolated by distillation or crystallization.
[b] Reactions run with 1–10 mol% triethylamine as base.
[c] Reactions run without organic base catalyst present.
[d] Product isolated by preparative H.P.L.C.
[e] Reaction run with a 4-fold excess of styrene.

0039-7881/82/0632-0508 $ 03.00

the types of reactants employed and the yields of products obtained. Our yields are quite good, and there are several cases where the biphasic method provides significant yield improvement over that reported in earlier literature. The fused bicyclic isoxazoline, **3g** produced by intramolecular cyclization from the oxime of 2-allyloxybenzaldehyde **(4)**[9], was isolated in 90% yield while other workers[10] obtained only a 42% yield.



Likewise, benzonitrile oxide generated from **5** biphasically in the presence of *N*-benzylidenemethylamine **(6)** gave a nearly quantitative yield of 3,5-diphenyl-4-methyl-Δ^2-1,2,3-oxadiazoline **(3h)**. Earlier workers[11] had obtained the oxadiazoline in 79% yield starting from the benzhydroxamic acid chloride.



3,5-Diphenyl-2-isoxazoline (3a); Typical Procedure for Intermolecular Additions:

To a 50-ml-Erlenmeyer flask containing styrene (2.13 g, 21 mmol), triethylamine (0.2 g, 1.98 mmol), dichloromethane (15 ml), and 11% aqueous sodium hypochlorite[7] (20 ml, 2.5 g NaOCl, 34 mmol) is added dropwise over 15 min with stirring at 0 °C, benzaldoxime (**1a**; 2.54 g, 21 mmol) in dichloromethane (10 ml). After stirring for 45 min, the reaction phases are separated and the aqueous phase is extracted with dichloromethane (3 x 15 ml). The combined organic layers are dried with magnesium sulfate and the solvent removed under reduced presure; yield of crude **3a**: 4.25 g (91%); pure by ^{1}H-N.M.R. spectrometry and T.L.C. analysis on Brinkman Silica Gel G, UV-254 5 x 10 cm analytical slides, dichloromethane as solvent, product $R_f = 0.49$; G.L.C. using a 6 feet x 1/8 inch SS column packed with 10% QF 1 on Chromosorb W-HP, $T_{col} = 120\,°C$ (2 min) programmed at 32 °C/min to 250 °C (8 min), product retention time = 8.59 min. This residue is recrystallized from 95% ethanol to give pure **3a**; yield: 3.31 g (71%); m.p. 73-75 °C (Ref.[12], m.p. 76 °C).

4*H*-[1]Benzopyrano[4,3-*c*]-2-isoxazoline (3g); Typical Procedure for Intramolecular Additions:

To 2-allyloxybenzaldoxime (**4**; 5.34 g, 30 mmol) and triethylamine (0.06 g, 0.59 mmol) in dichloromethane (45 ml) is added dropwise at 0 °C over 15 min, 11% aqueous sodium hypochlorite (45 ml, 5.39 g, NaOCl, 73 mmol). After stirring for 45 min, no starting oxime remains and the product is isolated as described above. The crude product is recrystallized from hexane; yield: 4.75 g (90%); m.p. 62-63 °C (Ref.[10], m.p. 62 °C).

Received: September 28, 1981
(Revised form: February 9, 1982)

---

[1] R. Huisgen, *Angew. Chem.* **75**, 604, 742 (1963); *Angew. Chem. Int. Ed. Engl.* **2**, 565, 633 (1963).

[2] C. Grundmann, *Synthesis* **1970**, 344.
C. Grundmann, P. Grünanger, *Nitrile Oxides*, Springer Verlag, New York-Heidelberg, 1971.

[3] A. Padwa, *Angew. Chem.* **88**, 131 (1976); *Angew. Chem. Int. Ed. Engl.* **15**, 123 (1976).

[4] C. Grundmann, R. Richter, *J. Org. Chem.* **33**, 476 (1968).
C. Grundmann, S. K. Datta, *J. Org. Chem.* **34**, 2016 (1969).

[5] G. A. Lee, H. H. Freedman, *Tetrahedron Lett.* **1976**, 1641.

[6] Grundmann and Dean have previously reported the use of alkali hypohalite, preferably hypobromite, to generate aromatic nitrile oxides which were stabilized by steric hindrance. C. Grundmann, J. M. Dean, *J. Org. Chem.* **30**, 2809 (1965).

[7] We have observed that several of the ylids can be generated and add to the dipolarophiles in a biphasic system which contains no amine. However, the yields of cycloaddition products are improved and reaction times are decreased when ~ 10 mol% of triethylamine is present.

[8] Swimming pool bleach: Typically contains 11.15% NaOCl, 12% NaCl, and 0.8% NaOH; pH ~ 13.

[9] 2-Allyloxybenzaldehyde was obtained from Pfaltz & Bauer, Inc. and converted to its oxime, m.p. = 41.5-42.5 °C.

[10] R. Fusco, L. Garanti, G. Zecchi, *Chim. Ind. (Milan)* **57**, 16 (1975).

[11] K. Bast, M. Christl, R. Huisgen, W. Mack, *Chem. Ber.* **105**, 2825 (1972).

[12] G. W. Perold, A. P. Steyn, F. V. K. von Reiche, *J. Am. Chem. Soc.* **79**, 462 (1957).

[13] G. Bianchi, P. Grünanger, *Tetrahedron* **21**, 817 (1965).

[14] G. F. Bettinett, C. Fraschini, *Gazz. Chim. Ital.* **100**, 403 (1970).

[15] R. Huisgen, W. Mack, *Tetrahedron Lett.* **1961**, 583.

[16] J. S. Clovis, A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich, V. Weberndörfer, *Chem. Ber.* **100**, 1593 (1967).

0039-7881/82/0632-0509 $ 03.00