

Quinuclidine *N*-oxide: a potential replacement for HMPA

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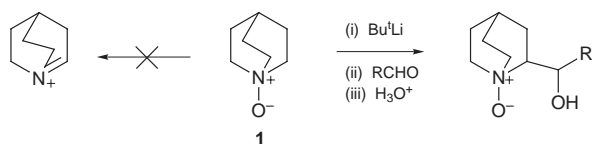
The use of quinuclidine *N*-oxide as a replacement for HMPA is described.

There are numerous significant and important reactions in organic synthesis which require the addition of hexamethylphosphoric triamide (HMPA) to render them viable.¹ HMPA is a dipolar aprotic compound with a superb ability to form cation–ligand complexes and it can enhance the rates of a wide variety of main group organometallic reactions. In addition, it can also influence the regio- and stereo-chemistry of key reactions such as enolate formation. Other reactions in which HMPA can enhance reactivity include carbanion formation, carbanion reactivity, carbanion regioselectivity (1,2 vs. 1,4 addition), ylide reactivity and anion reactivity. In essence, it is thought that HMPA acts as a metal binding agent, disrupting the aggregation states that enolates normally exist in.²

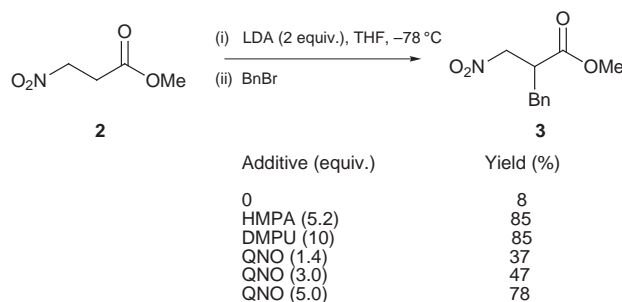
HMPA is a listed mutagen and as such does not find widespread use either in industry or academia. Several other substances, such as 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (DMPU) have been used as replacements but all have their limitations.³ An amine oxide bears the same type of charge distribution as a phosphine oxide, but the dipole moment is much larger. Therefore an amine oxide would be expected to behave in a similar fashion to a reagent such as HMPA. The major problem lies with the instability of most amine oxides towards strong bases, azomethine ylide formation being the most common pathway.⁴

As a consequence of our previous work with amine oxides,⁵ we have carried out preliminary studies using quinuclidine *N*-oxide (QNO) as a replacement for HMPA, since it is an amine oxide that is known to be stable in strongly basic conditions. Indeed, it can be deprotonated with Bu^tLi and the corresponding anion can be reacted with aldehydes and ketones.⁶ This amine oxide is stable because elimination of lithium oxide would lead to a bridgehead iminium ion (anti-Bredt) (Scheme 1).

We chose to study four key reactions in which HMPA is known to play a vital role and we have investigated the effect of replacing the HMPA by quinuclidine *N*-oxide. The reactions examined were enolate alkylation,⁷ 1,4 vs. 1,2 addition,⁸ diastereoselective nitroaldol reactions⁹ and epoxide opening.¹⁰ Quinuclidine *N*-oxide has been prepared by the oxidation of quinuclidine with 30% H₂O₂ in MeOH.¹¹ However, we routinely use MCPBA as the oxidant as it is more convenient on a laboratory scale.¹² The product can be purified by chromatography on silica gel. The product is dried under vacuum over P₂O₅. It is a hygroscopic solid and needs to be stored under vacuum over P₂O₅. The quinuclidine nucleus is ideal since it is a rigid structure amenable to rapid modification. In addition, a number of functionalised derivatives can be readily made, some in chiral form.¹³



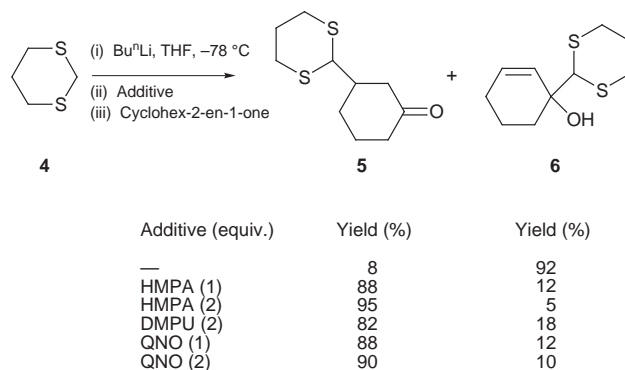
Scheme 1



Scheme 2

Our investigations started with the alkylation of the dianion of methyl 3-nitropropionate, a reaction that is known to require 5 equiv. of HMPA to proceed in good yield. It was found that with just 3 equiv. of QNO the required product was isolated in a reasonable 47%, and the use of 5 equiv. gave a yield comparable to that with HMPA (Scheme 2).

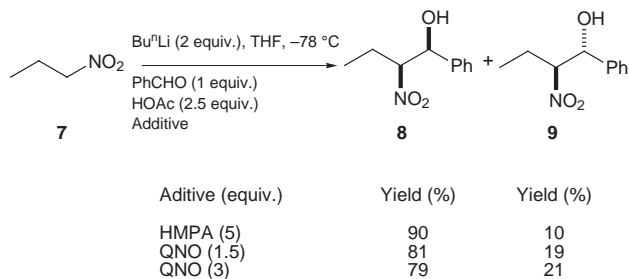
We next examined the regioselectivity of addition of 2-lithiodithiane to cyclohex-2-en-1-one. In the absence of HMPA the predominant mode of addition is 1,2. When 1 equiv. of HMPA is added the 1,4 addition product becomes the major one.⁸ Addition of QNO switched the reaction to give the 1,4 addition product with good selectivity (Scheme 3). Indeed, it was considerably more selective than the use of DMPU.



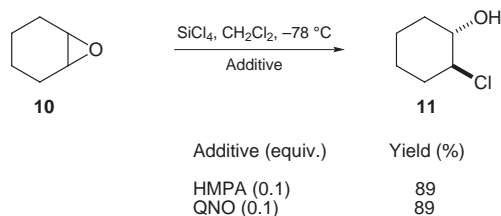
Scheme 3

We then studied the addition of the dianion of 1-nitropropane to benzaldehyde. This gives the nitroaldol products as a mixture of diastereoisomers. In the presence of HMPA, the *syn* diastereoisomer is the major product.⁹ The addition of 1.5 equiv. of QNO was also found to promote formation of the *syn* diastereoisomer giving a 4:1 mixture of diastereoisomers in 62%. The addition of more QNO did not appear to improve the selectivity (Scheme 4).

Finally, Denmark and co-workers have recently reported the use of HMPA and SiCl₄ to cleave epoxides to give chlorohydrins.¹⁰ With a chiral phosphinamide, the ring opening of *meso* epoxides gave enantiomerically enriched chlorohydrins. It was gratifying to find that QNO mediated the ring opening of cyclohexene oxide to give the chlorohydrin in a yield identical



Scheme 4



Scheme 5

to that obtained using HMPA. In the absence of QNO the chlorohydrin was isolated in low yield (Scheme 5).

Significantly, QNO was found to be negative in the bacterial reverse mutation test conducted on *Salmonella typhimurium* TA98, TA100 and TA102 in the presence or absence of metabolic activation. Additionally it was also found to be negative in the test to evaluate its potential to induce micronuclei in Chinese hamster ovary cells using the cytokinesis block method in the presence or absence of metabolic activation.

In summary, we have shown that quinuclidine *N*-oxide can act as a replacement for HMPA in a range of reactions.¹⁴ We are currently exploring other reactions known to require HMPA, and synthesising second generation quinuclidine *N*-oxides which are chiral and bear additional metal binding sites for enhanced reactivity and solubility. Their properties, applications and use in a range of asymmetric transformations will be reported shortly.

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Notes and references

- R. R. Dykstra, *Encyclopedia of Organic Reagents*, ed. L. Paquette, 1995, vol. 4, p. 2668.
- D. Seebach, *Angew. Chem., Int Ed. Engl.*, 1988, **27**, 1624.
- T. Mukhopadhyay and D. Seebach, *Helv. Chim. Acta.*, 1982, **65**, 385.
- R. Beugelmans, L. Benadjila-Iguertsira and G. Roussi, *J. Chem. Soc., Chem. Commun.*, 1982, 544; G. Roussi and J. Zhang, *Tetrahedron*, 1991, **47**, 5161.
- I. A. O'Neil, N. D. Miller, J. Peake, J. V. Barkley, C. M. R. Low and S. B. Kalindjian, *Synlett*, 1993, 515; I. A. O'Neil, N. D. Miller, J. V. Barkley, C. M. R. Low and S. B. Kalindjian, *Synlett*, 1995, 617 and 619; I. A. O'Neil, C. D. Turner and S. B. Kalindjian, *Synlett*, 1997, 777; I. A. O'Neil and A. J. Potter, *Tetrahedron Lett.*, 1997, **38**, 5731; I. A. O'Neil and A. J. Potter, *Chem. Commun.*, 1998, 1487.
- D. H. R. Barton, R. Beugelmans and R. N. Young, *Nouv. J. Chim.*, 1978, **2**, 363.
- D. Seebach, R. Henning and T. Mukhopadhyay, *Chem. Ber.*, 1982, **115**, 1705.
- C. A. Brown and A. Yamaichi, *J. Chem. Soc., Chem. Commun.*, 1979, 101.
- F. Lehr, J. Gonnermann and D. Seebach, *Helv. Chim. Acta.*, 1979, **62**, 2259.
- S. E. Denmark, P. A. Barsanti, K. T. Wong and R. A. Stavenger, *J. Org. Chem.*, 1998, **63**, 2428; S. E. Denmark, D. M. Coe, N. E. Pratt and B. D. Griedel, *J. Org. Chem.*, 1994, **59**, 6161.
- S. Srinivas and K. G. Taylor, *J. Org. Chem.*, 1990, **55**, 1779; H. C. Kolb, P. G. Andersson and K. B. Sharpless, *J. Am. Chem. Soc.*, 1994, **116**, 1278.
- J. C. Craig and K. K. Purushothaman, *J. Org. Chem.*, 1970, **35**, 1721.
- K. A. Bairamov, A. G. Douglass and P. Kaszynski, *Syn. Commun.*, 1998, **28**, 527; M. Langlois, C. Meyer and J. L. Soulier, *Syn. Commun.*, 1992, **22**, 1895.
- Alkylation of methyl 3-nitropropanoate: A solution of diisopropylamine (0.9 ml, 0.63 mmol) and quinuclidine *N*-oxide (1.78 g, 14 mmol) in dry THF (40 ml) was cooled to -78°C . To this solution was added BuLi (4.0 ml, 1.6 M in hexane, 0.63 mmol). The solution was stirred for 30 min, then methyl 3-nitropropanoate (0.37 g, 2.8 mmol) was added. After stirring for 60 min benzyl bromide (0.4 ml, 0.35 mmol) was added. The solution was stirred for 5 h. Acetic acid (1.0 ml, 2.8 mmol) was added followed by distilled water (5.0 ml). The solution was warmed to room temperature and water (50 ml) was added. Diethyl ether (50 ml) was added, the organic layer separated and the aqueous layer extracted with diethyl ether (3×50 ml). The combined organic layers were washed with water (100 ml), and dried over MgSO_4 . The solvent was removed *in vacuo*. The crude reaction mixture was purified by flash chromatography over silica gel eluting with EtOAc–light petroleum (bp $40\text{--}60^{\circ}\text{C}$), 1 : 9 to give the desired product (0.48 g, 78%). The aqueous layer contains the quinuclidine *N*-oxide.

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