N-(1'-Benzotriazolylmethyl)-5-phenylmorpholin-2-one: A Stable Crystalline Chiral Azomethine Ylid Precursor

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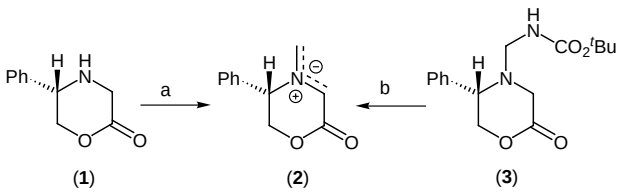
Abstract: The crystalline adduct of (5*S*)-5-phenylmorpholin-2-one with formaldehyde and benzotriazole on treatment with acid generates an azomethine ylid which may be trapped with a range of dipolarophiles in yields superior to those using in situ generation methodology.

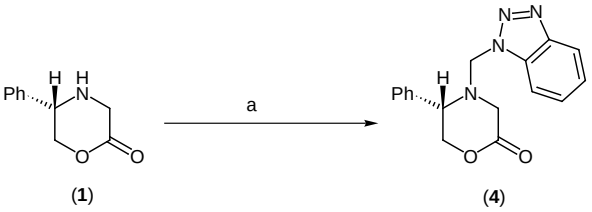
Key words: chiral, azomethine ylid, benzotriazole, dipolar cycloaddition

In a series of papers we have reported that (5*S*)-5-phenylmorpholin-2-one **1** reacts with aldehydes under both thermal[2a–l] or Lewis acid catalysed conditions,[3] generating the azomethine ylid species **2** capable of undergoing highly diastereoselective cycloadditions. In an effort to extend the utility of this methodology we have pursued a programme to identify stable substrates, which would furnish **2** under milder and experimentally more convenient conditions. This has resulted in the identification of carbamate derivative **3**, which although it satisfied the chemical and physical criteria, was not competitive with the direct generation procedure in terms of yields of cycloadducts (Scheme 1).[4]



Scheme 1 a) $(HCHO)_n$, toluene, reflux, $-H_2O$; b) TFA, THF, r.t.

Aware of the comprehensive studies of Katritzky detailing the reactivity profile of benzotriazole derivatives,[5] we decided to explore the potential of this functionality within the context of azomethine ylid generation. Accordingly, following Katritzky's procedure,[6] (5*S*)-5-phenyl morpholin-2-one **1** and benzotriazole were dissolved in 1:1 aqueous ethanol, aqueous formaldehyde added and the mixture left at room temperature overnight. This resulted in the precipitation of *N*-(1'-benzotriazolylmethyl)-5-phenyl morpholin-2-one **4** as a colourless solid, isolated in 78% yield (Scheme 2).[7]



Scheme 2 a) benzotriazole, 32% aq HCHO, 1:1 EtOH:H_2O, r.t., 24h

In previous studies, *N*-phenylmaleimide and *N*-methylmaleimide have been found to be consistently the most effective dipolarophiles for cycloadditions onto azomethine ylids derived from **1** and hence these were chosen to determine optimal reaction conditions. A survey of various alkylating, Lewis acid and Brønsted acid promoters such as MeI, $BF_3{\cdot}Et_2O$, trifluoroacetic acid, pyridinium *para*-toluenesulfonate and *para*-toluenesulfonic acid in a series of solvents and over a range of temperatures and reaction times led to adoption of *para*-toluenesulfonic acid in refluxing THF for 24 hours as the favoured conditions.[8] Although most combinations led to isolation of cycloadducts, these optimal conditions gave combined yields of *exo*- and *endo*-cycloadducts superior to the standard protocol in which the ylid is generated directly from **1** using paraformaldehyde in refluxing toluene. Applying these optimised conditions to other dipolarophiles similarly gave equal or superior yields to the standard protocol (Scheme 3). Due to apparent incompatibility with the standard thermal conditions, dimethyl fumarate had previously been found not to furnish any cycloadduct but modifying the optimised conditions with **4**, using chloroform as solvent, gave a single cycloadduct in 50% yield. In keeping with previous observations, methyl propynoate gave the regioisomer to be expected from $LUMO_{dipole}$–$HOMO_{dipolarophile}$ frontier orbital interaction, whereas other monoactivated dipolarophiles failed to react. The similarity in yields, scope and limitation of this new approach with those of the standard procedure leads us to conclude that the reacting dipolar species are very similar under both sets of reaction conditions and that the benzotriazole must be totally divorced from the substrate before any significant bonding interaction occurs with the dipolarophile.

In conclusion, we have demonstrated that (5*S*)-*N*-(1'-benzotriazolylmethyl)-5-phenyl morpholin-2-one **4** satisfies the criteria of providing a stable, solid material which generates azomethine ylid **2** under mild conditions which per-

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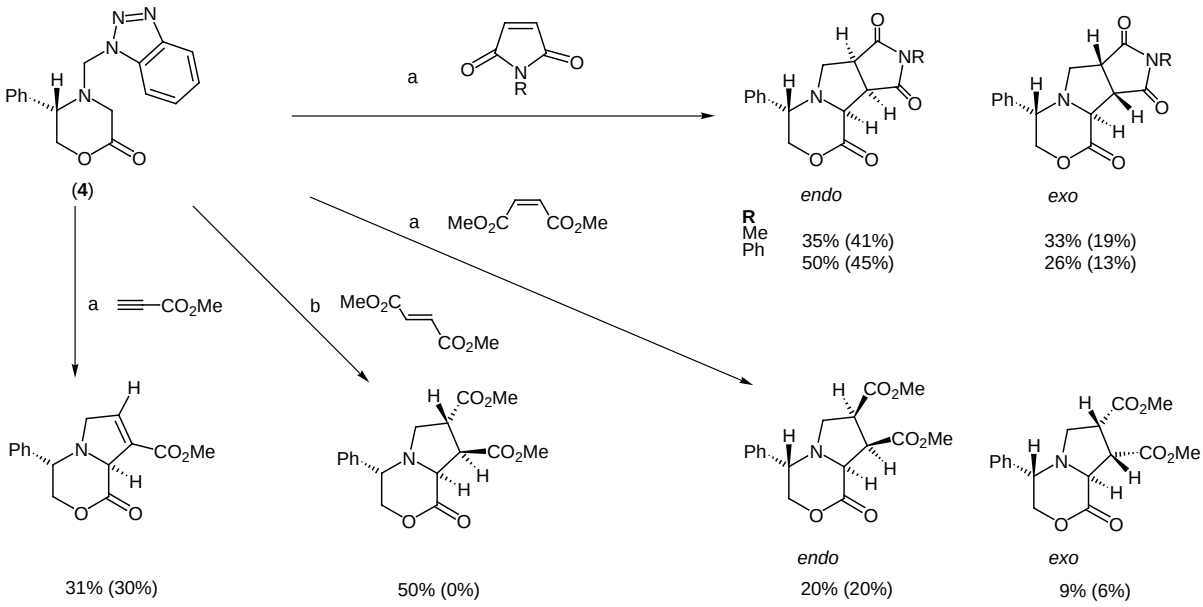

Scheme 3 a) PTSA, THF, reflux, 24 h; b) PTSA, $CHCl_3$, reflux, 24 h. Yields in parentheses are those obtained by generating the ylid directly from morpholinone under standard thermal conditions.[2a–d]

mit efficient trapping with a range of doubly activated dipolarophiles.

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(7) **(5*S*)-*N*-(1'-Benzotriazolylmethyl)-5-phenylmorpholin-2-one(4)**: (5*S*)-5-Phenylmorpholin-2-one **1** (474 mg, 2.7 mmol, 1 equiv) and benzotriazole (319 mg, 2.7 mmol, 1 equiv) were dissolved in water–ethanol 1:1 (5 mL). Formaldehyde (37 wt% solution in water, 0.2 mL, 1 equiv) was added via syringe and the resulting solution was stirred at r.t. overnight. The solution was then cooled to 5 °C and the resultant precipitate was filtered and washed with 1:1 aq ethanol and dried in vacuo giving a colourless solid (645 mg, 78%), mp 112–113 °C; $[\alpha]^{19}_{D}$ +82.0 (c 0.75, $CHCl_3$); (Found C, 65.92; H, 5.25; N, 17.94. $C_{17}H_{16}N_4O_2$ requires C, 66.22; H, 5.23; N, 18.16%.); ν_{max} (KBr disc): 175, 1456 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ = 8.05 (1 H, d, *J* = 8.2 Hz), 7.69 (1 H, d, *J* = 8.2 Hz), 7.55–7.38 (7 H, m), 5.64 (1 H, d, *J* = 14.7 Hz), 5.40 (1 H, d, *J* = 14.7 Hz), 4.30–4.46 (4 H, m), 3.66 (1 H, d, *J* = 16.8 Hz) ppm; ^{13}C NMR (100 MHz, DMSO): δ = 168.5, 144.6, 137.3, 133.5, 128.6, 128.3, 128.2, 128.0, 127.9, 123.9, 118.9, 110.4, 70.7, 63.9, 57.6, 50.2 ppm; MS (C.I.): *m/z* 120 [$C_6H_6N_3^+$], 90.

(8) **General Method for the Preparation of Cycloadducts**: *N*-(1'-Benzotriazolylmethyl)-5-phenylmorpholin-2-one **4** (1 equiv), dipolarophile (3 equiv) and *para*-toluenesulfonic acid (0.5 equiv) were dissolved in dry THF, or in the case of dimethyl fumarate, in dry chloroform. Subsequently, the mixture was refluxed for 24 h. Removal of solvent in vacuo yielded the crude mixture of products along with excess dipolarophile. The cycloadducts were then purified by column chromatography on silica, eluting with toluene/diethyl ether. Identification of the cycloadducts was carried out by comparison with the known products.[2]