N-Amino-*N*-methylmorpholinium Salts: Highly Active Aziridination Reagents for Chalcones

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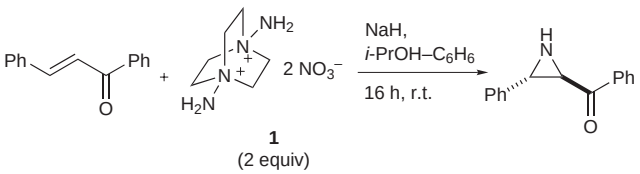
Abstract: A highly effective aziridination reagent, based on *N*-methylmorpholine, is reported which effects rapid conversion of chalcones to N-unfunctionalised aziridines at room temperature.

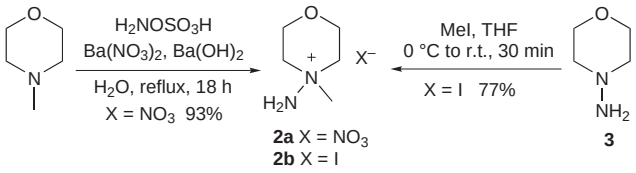
Key words: aziridine, hydrazinium salts, chalcone, aminimine

Aziridines are highly attractive synthetic intermediates,[2] largely because they can undergo ring opening with a variety of nucleophiles to give functionalised amine products.[3,4] However, alkene aziridination, particularly asymmetric aziridination, is far less well developed than the closely related epoxidation.[5–8] We were attracted by the report of Xu in 2002 that enones can be aziridinated by hydrazinium salt **1** in the presence of NaH (Scheme 1).[9] By analogy with an earlier study,[10] this chemistry was assumed to proceed by deprotonation of **1** to give an N–N ylid (aminimine), which then undergoes Michael addition to the enone followed by ring closure to give the aziridine. An advantage of the method is that it affords N-unsubstituted aziridines which allows flexibility in further functionalising the nitrogen with a choice of activating group. We reasoned that this process had potential for asymmetric aziridination if chiral hydrazinium salts were employed. However, the strong base and carcinogenic solvent employed in this work were unattractive, as were the relatively long reaction times. Therefore, we undertook a study of alternative reaction conditions and report here the discovery of two new base systems as well as a more reactive hydrazinium salt that is particularly convenient to prepare.

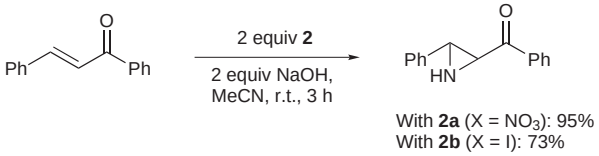


Scheme 1

We began by testing the Xu nitrate salt **1** (2 equiv) for aziridination of chalcone with alternative bases and solvents. Early studies showed that it was possible to use NaOH in MeCN, but the yield of aziridine was low (17% after 18 h). Therefore we prepared alternative hydrazinium nitrate salts by amination of several cyclic amines. While the hydrazinium salts derived from *N*-methylpyrrolidine and *N*-methylpiperidine gave comparable or lower yields of aziridine, we were delighted to find that the *N*-methylmorpholinium nitrate salt **2a** (Scheme 2), prepared by amination of *N*-methylmorpholine (Scheme 2), effected aziridination of chalcone in 95% yield after only three hours under the NaOH/MeCN conditions (Scheme 3). While this result was encouraging, particularly in identifying the reactivity of the morpholine framework, we felt that the procedure used to prepare the hydrazinium nitrate salt **2a** from *N*-methylmorpholine was inconvenient since it required reaction with hydroxylamine-*O*-sulfonic acid (HOSA) and $Ba(NO_3)_2$ over extended time periods at raised temperatures. Therefore, we were pleased to find that the corresponding iodide salt could be more readily prepared simply by treatment of commercially available *N*-aminomorpholine **3** with one equivalent of iodomethane in THF at 0 °C. The hydrazinium iodide salt **2b** was isolated after filtration as a white solid in 77% yield and can be further purified by recrystallisation from EtOH. Under the same NaOH/MeCN conditions, the iodide **2b** afforded a slightly lower yield of aziridine than nitrate **2a** (Scheme 3). This, along with the fact that the chemistry still required two equivalents of **2**, prompted us to screen further bases with the more readily accessed iodide **2b**.



Scheme 2



Scheme 3

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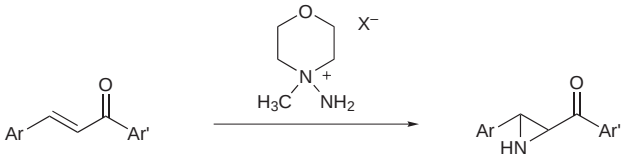
Reasoning that a homogeneous system may lead to improved reaction rates, we were pleased to find that *t*-BuOK in DMSO[11] allowed extremely rapid aziridination: consumption of chalcone was complete in five minutes, and the aziridine was isolated in 61% yield. Moreover, we could now use about one equivalent of **2b**. In view of the ease of preparation of **2b** and the rapid reaction times, we tested these new conditions with a range of enone substrates (Table 1, Method A). For some substrates, the NaOH/MeCN conditions were also tested for comparison (Table 1, Method B). Good yields of aziridine could be obtained for chalcone itself (Table 1, entries 1 and 2) and for a range of substituted derivatives (Table 1, entries 3–17). In all cases, the *trans*-aziridine was obtained predominantly (>90:10). Interestingly, Methods A and B displayed potentially useful differences in reactivity. Chalcones with the electron-donating MeO substituent gave better results with **2b** and *t*-BuOK/DMSO (Table 1, entry 7 vs 8; entry 15 vs 16), while some electron-poor chalcones afforded higher yields with the **2a**/NaOH/MeCN system (Table 1; entry 10 vs 11, entry 12 vs 13). This may indicate mechanistic differences between the two systems: indeed, intense colour changes were observed during the successful reactions with **2b**/*t*-BuOK/DMSO, and electron-transfer processes have been reported under similar conditions.[12] Such mechanistic detail will be the subject of future investigations. Pleasingly, we were also able to extend the methodology to other aromatic systems such as 1-napthyl and 3-furyl chalcones in comparable yield (Table 1, entries 18 and 19), with Method A again giving better results for the latter, electron-rich substrate (Table 1, entry 19 vs 20). Unfortunately, however, we have so far not been able to extend the substrate scope to include alkyl-substituted enones: no aziridine has been obtained from cyclohexenone, benzylidene acetone or 1-phenylbut-2-en-1-one.

In conclusion, we have developed a convenient new reagent system for aziridination of chalcones. Efforts to extend the scope and mechanistic detail of the chemistry, to develop an asymmetric variant by use of chiral hydrazinium salts, and to explore synthetic applications of the aziridine products are currently underway.

Table 1 Enone Aziridination[13]



Entry	Ar	Ar′	Method[a]	Isolated yield (%)
1	Ph	Ph	A	61
2	Ph	Ph	B	95
3	*o*-MeC_6H_4	Ph	A	68
4	*o*-$MeOC_6H_4$	Ph	A	65
5	*o*-ClC_6H_4	Ph	A	55
6	*p*-MeC_6H_4	Ph	A	60
7	*p*-$MeOC_6H_4$	Ph	A	56
8	*p*-$MeOC_6H_4$	Ph	B	2
9	*p*-ClC_6H_4	Ph	A	42
10	*p*-CNC_6H_4	Ph	A	0
11	*p*-CNC_6H_4	Ph	B	17
12	*m*-$NO_2C_6H_4$	Ph	A	0
13	*m*-$NO_2C_6H_4$	Ph	B	83
14	Ph	*p*-MeC_6H_4	A	58
15	Ph	*p*-$MeOC_6H_4$	A	67
16	Ph	*p*-$MeOC_6H_4$	B	9
17	Ph	*p*-ClC_6H_4	A	48
18	1-naphthyl	Ph	A	59
19	3-furyl	Ph	A	64
20	3-furyl	Ph	B	7

[a] Method A: enone (1 equiv), **2b** (1.1 equiv), DMSO, *t*-BuOK (1.1 equiv), 5 min, r.t. Method B: enone (1 equiv), **2a** (2 equiv), MeCN, NaOH (2 equiv), 18 h, r.t.

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(13) **Compound 2a**: $Ba(NO_3)_2$ (10.3 g, 40 mmol), $Ba(OH)_2$ (12.5 g, 40 mmol) and *N*-methyl morpholine (4.4 mL, 40 mmol) were added to H_2O (60 mL) to give a turbid white mixture. This was added in 2-mL portions to a solution of hydroxylamine-*O*-sulfonic acid (5.6 g, 50 mmol) in H_2O (50 mL) to give a white precipitate immediately. The mixture was then heated at reflux for 18 h. The white precipitate was filtered off and the filtrate was concentrated under reduced pressure leaving a white crystalline solid. This solid was then recrystallised (H_2O) to give the hydrazinium nitrate salt **2a** (7.13 g, 99%) as a white solid. ^{1}H NMR (400 MHz, DMSO): δ = 5.96 (2 H, br, NH_2), 3.99–3.93 (2 H, m, OCH_2), 3.87–3.82 (2 H, m, OCH_2), 3.59–3.53 (2 H, m, NCH_2), 3.44–3.52 (2 H, m, NCH_2), 3.33 (3 H, s, NCH_3). ^{13}C NMR (100 MHz, DMSO): δ = 62.2 (CH_2), 60.4 (CH_2), 56.6 (CH_3).
Compound 2b: To a solution of *N*-aminomorpholine (8.9 mL, 92 mmol, 1.0 equiv) in THF (60 mL) at 0 °C was added neat MeI (6.0 mL, 96 mmol, 1.05 equiv) dropwise over 5 min. During this time, a white precipitate was observed to form and after completion of the addition of MeI, the reaction mixture was warmed to r.t. for 30 min. Et_2O (100 mL) was added and the white solid was isolated by filtration and subsequently washed with Et_2O (4 ×). The morpholinium iodide salt **2b** (17.18 g, 77%) was isolated as a white powder which was recrystallised from hot EtOH–MeOH (3:1) to give clear plates. ^{1}H NMR (400 MHz, DMSO): δ = 5.97 (2 H, s, NH_2), 3.96 (2 H, ddd, *J* = 13.2, 9.2, 3.9 Hz, CH_2), 3.86 (2 H, dt, *J* = 12.8, 3.2 Hz, CH_2), 3.60 (2 H, ddd, *J* = 12.8, 9.2, 3.2 Hz, CH_2), 3.48 (2 H, br d, *J* = 12.4 Hz, CH_2), 3.41 (3 H, s, CH_3). ^{13}C NMR (100 MHz, DMSO): δ = 62.4, 60.1, 56.4.
Aziridination of *E*-Chalcones; General Procedure
Method A: Chalcone (0.20 g, 0.96 mmol) and morpholinium iodide **2b** (0.24 g, 1.05 mmol, 1.1 equiv) were dissolved in DMSO (10 mL) at r.t. To this solution was added solid *t*-BuOK (0.12 g, 1.07 mmol, 1.1 equiv) in 10 portions over 1 min. During this addition a bright red colour forms. After 5 min, H_2O (50 mL) and Et_2O (50 mL) were added. The reaction was extracted with Et_2O (100 mL) and washed with H_2O (2 × 100 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed in vacuo. The crude product was further purified on silica gel (PE–Et_2O, 4:1) to give the aziridine (0.13 g, 61%) as a fine white solid; mp 100–101 °C. IR (KBr): 3268 (NH), 1668 (C=O) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.00–7.20 (10 H, m, Ar), 3.52 (1 H, dd, *J* = 7.9, 2.4 Hz), 3.18 (1 H, dd, *J* = 9.2, 2.4 Hz), 2.68 (1 H, t, *J* = 8.5, NH). MS (CI): *m*/*z* (%) = 224 (M + H, 100).
Method B: *N*-Methyl-*N*-aminomorpholinium nitrate (**2a**, 0.17 g, 0.96 mmol) and NaOH (0.04 g, 0.96 mmol) were added to MeCN (4 mL) and the resulting solution was stirred at r.t. for 30 min. Chalcone (0.10 g, 0.48 mmol) was then added and the mixture was stirred for a further 3 h. The reaction was then quenched with a sat. solution of NH_4Cl (20 mL) and extracted with toluene (3 × 20 mL). The organic layers were then washed with a sat. solution of NH_4Cl (20 mL), dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was further purified on silica gel (PE–Et_2O, 4:1) to give the aziridine (0.10 g, 95%); data as above.
NMR data for aziridine products in Table entries 1, 2, 4–9,[9] 10, 11,[6] and 14–17[9] corresponded to those in the literature. Other aziridines also gave satisfactory spectroscopic data in accord with their assigned structures.
Caution. While no problems were encountered during our work, hydrazinium salts should be considered as potentially hazardous and should be handled with appropriate precautions. Differential scanning calorimetry studies indicated an exotherm for iodide salt **2b** at ca. 170 °C; no exotherm was noted for nitrate **2a** at temperatures up to 300 °C.