Selective Alkylation of β-Ketoester Enolates using *O*-Methyl Aminosulfoxonium salts; the First Example of C-alkylation using Sulfoxonium Salt Electrophiles

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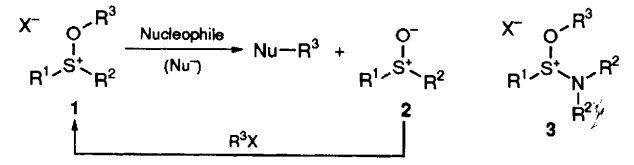
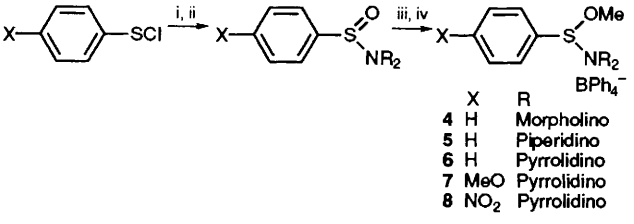
The alkylation of β-ketoester enolates with *O*-methyl aminosulfoxonium tetraphenylborate salts is reported; good to excellent selectivity for C- *vs.* O-alkylation is observed, and is found to be dependent on the nature of the β-ketoester, solvent, metal counterion and aminosulfoxonium salt.

The alkylation of enolate anions with carbon electrophiles is one of the fundamental synthetic methods for the formation of new carbon–carbon bonds. The development of related procedures for preparation of enantiomerically pure compounds using chiral auxiliaries,[1,2] phase transfer catalysis,[3] organometallic chemistry[4] and chiral bases[5] is now well established, but there are inherent problems due to the need for stoichiometric amounts of reagent and/or generality. An alternative approach involves the use of electrophilic reagents which have a homochiral leaving group.[6–8] This has the advantage that no chiral auxiliary has to be removed from the product at the end of the reaction, and as the leaving group is often a precursor to the active electrophile, it may be possible to adapt the reaction such that it only requires a catalytic amount of the chiral leaving group. Our interest in novel sulfoxonium salts[9] has led us to consider related compounds as chiral electrophiles. It has been previously reported that *O*-methyl sulfoxonium salts (**1**, R^1 = *p*-tolyl, R^2 = R^3 = Me) react with nucleophiles such as amines and sulfides, in a transalkylation reaction, to give a sulfoxide **2** and the alkylated nucleophile (Scheme 1),[10] in some cases with significant enantioselectivity.[11,12] Herein we report the first examples of selective alkylation at carbon using *O*-methyl aminosulfoxonium salts **3** and nucleophiles derived from β-ketoesters, along with some preliminary studies on the factors affecting such alkylations. This work now provides the basis for asymmetric alkylation procedures which are currently under development in our laboratories.[13]

We have adapted the procedure originally reported by Minato *et al.*[12] to prepare a number of known **4** and novel **5–8** *O*-methyl aminosulfoxonium salts, by preparation and subsequent alkylation of appropriate sulfinamide precursors (Scheme 2). Thus treatment of an arylsulfenyl chloride[14] with the required amine, and oxidation (*m*-CPBA) gave the sulfinamide, which was methylated using methyl trifluoromethane-sulfonate to give the *O*-methyl aminosulfonium triflates which could be isolated as pale yellow oils. Anion exchange using sodium tetraphenylborate gave the aminosulfoxonium tetraphenylborates, generally as colourless crystalline solids, which are indefinitely stable when stored at +4 °C or below† and were chosen as our representative salts for initial investigations on the grounds of reproducibility and ease of handling.



Scheme 1



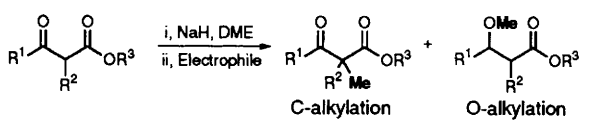
	X	R
4	H	Morpholino
5	H	Piperidino
6	H	Pyrrolidino
7	MeO	Pyrrolidino
8	NO_2	Pyrrolidino

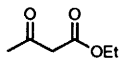
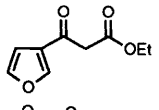
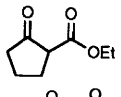
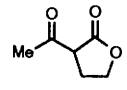
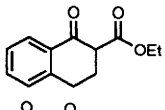
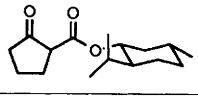
Scheme 2 *Reagents and conditions*: i, R_2NH (2 equiv.), >90% yield; ii, *m*-CPBA, CH_2Cl_2, 70–80% yield; iii, MeOTf, $MeNO_2$; iv, $NaBPh_4$, 70–90% overall yield

With the *O*-methyl aminosulfoxonium salts in hand, we then began to investigate their reactions with a variety of carbon nucleophiles. After initially disappointing results with simple ketone enolates and enamines, we were gratified to discover that salts such as **6** reacted smoothly with sodium enolates derived from β-ketoesters with good to excellent selectivity for C- *vs.* O-alkylation, in 70–84% isolated yield‡ (Table 1). These are, to the best of our knowledge, the first examples of C-alkylation using sulfoxonium salts in a transalkylation reaction, although sulfonium salts (R_3S^+) have been used in a related reaction.[15] Importantly, in all cases shown in Table 1, the sulfinamide leaving group can be recovered in good yield. For example, in the alkylation of menthyl 2-oxocyclopentanecarboxylate[16] with racemic salt **6** (entry 8), the C- and O-alkylated products can be isolated in 56% (12% d.e.) and 28% yields respectively, along with the recovered sulfinamide (80% yield) after chromatography.§

As can be seen from Table 1, increasing substitution between the carbonyl groups decreases the tendency for alkylation at carbon. For unsubstituted systems (entries 1 and 2) almost exclusive C-alkylation is observed. We chose ethyl

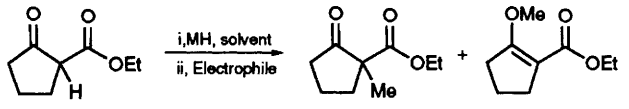
Table 1 Effect of β-ketoester structure on alkylation



Entry	β-Ketoester	Electrophile	Ratio C:O
1		**6**	1:0
2		**6**	1:0
3		**6**	1:0
4		MeOTf	1:2.5
5		MeI	1:0
6		**6**	3:0
7		**6**	2.5:1
8		**6**	2:1[a]

[a] 12% d.e. for *C*-alkylated product.

Table 2 Effect of solvent, cation and aminosulfoxonium salt structure on alkylation of ethyl 2-oxocyclopentanecarboxylate



Entry	Base	Solvent	Electrophile	Ratio C : O
1	NaH	MeCN	**6**	4 : 1
2	NaH	THF	**6**	3 : 1
3	NaH	THF (50 °C)	**6**	4 : 1
4	NaH	Bu^{t}OH (50 °C)	**6**	8 : 1
5	NaH	CH_2Cl_2	**6**	[a]
6	NaH	1,4-dioxane	**6**	[a]
7	NaH	DMF	**6**	1 : 1.5
8	NaH	DMSO	**6**	1 : 2
9	NaH	DME	**6**	3 : 1
10	LiH	DME	**6**	3 : 1
11	KH	DME	**6**	3 : 1
12	KH/18-crown-6	DME	**6**	1 : 2
13	EtMgBr[21]	THF	**6**	[a]
14	NaH	DME	**7**	3 : 1
15	NaH	DME	**8**	2 : 1
16	NaH	DME	**4**	3 : 1
17	NaH	DME	**5**	3 : 1

[a] No reaction observed.

2-oxocyclopentanecarboxylate (entry 3) as the candidate for our further studies, as it gave good C-selectivity but also appreciable O-alkylated product, an authentic sample of which was easily synthesised using methyl trifluoromethane sulfonate as electrophile (entry 4). It can be seen that our sulfoxonium salts are of intermediate selectivity for C- *vs.* O-alkylation when compared to methyl triflate and methyl iodide (entries 3–5).

We then began to investigate other factors which would be expected to influence the selectivity of this reaction. Solvents of moderate polarity (*e.g.* MeCN, DME, THF) gave similar C : O ratios which could be slightly improved by elevating the temperature. However, highly polar aprotic solvents such as DMF and DMSO showed a reversal of selectivity in favour of O-alkylation as would be expected from literature precedent of general enolate alkylation reactions.[17] The effect of metal counterion was also investigated. There was relatively little difference between Li, Na and K, however the more naked enolate generated using KH/18-crown-6 (entry 12, Table 2) showed enhanced O-alkylation, again in accord with previous studies on enolate alkylation.[17,18] Unfortunately, magnesium enolates, which often give high selectivity for C-alkylation,[19] were too unreactive for our electrophiles (entry 13). For other reactions where no reaction was observed (entries 5 and 6) we believe the problem was one of solubility of the enolate and/or the aminosulfoxonium salt.

Electron-withdrawing **8** and -donating **7** groups in the aromatic ring of the aminosulfoxonium salt also showed interesting effects. The *p*-nitro substituted salt **8** was significantly more reactive than **6**, and was also correspondingly less stable. It showed enhanced O-alkylation, as would be expected for a more reactive electrophile. In contrast, the *p*-methoxy substituted salt **7** was significantly less reactive than **6**, taking a longer period of time for the alkylation reaction to reach completion, with a slight increase in selectivity for C-alkylation.[17]

In conclusion, we have demonstrated that aminosulfoxonium salts can be used as electrophilic reagents for C–C bond formation by alkylation of β-ketoester anions. The reaction conditions, salt and substrate structure can be varied to influence the selectivity in such an alkylation reaction. We are now investigating the potential of homochiral aminosulfonium salts as asymmetric alkylating agents, the results of which will be published in due course.

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Footnotes

† An exception was the salt **8**, which was somewhat unstable, decomposing over a period of hours at room temp.

‡ With more volatile β-ketoesters, *e.g.* ethyl acetoacetate (entry 1, Table 1), the isolated yields were somewhat lower due to practical difficulties in working with these substrates, however the alkylation reactions themselves were very clean (>90% alkylation) as indicated by ^{1}H NMR.

§ All new compounds were characterised by ^{1}H and ^{13}C NMR, IR and mass spectra and gave satisfactory elemental analyses and/or accurate mass spectra. Ratios shown in Tables 1 and 2 were determined from the ^{1}H and/or ^{13}C NMR spectra of the crude product mixture.

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