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Reaction of α-amidoalkylphenyl sulfones with Reformatsky reagents. A new entry to β-amino esters

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Abstract

The reaction of Reformatsky reagents with α-amidoalkylphenyl sulfones proceeds in dichloromethane at room temperature leading to the synthesis of the corresponding β-amino esters in good yields. The procedure presents *syn* stereoselectivity and can be also extended to Reformatsky reagents based on γ-bromocrotonates. © 2000 Elsevier Science Ltd. All rights reserved.

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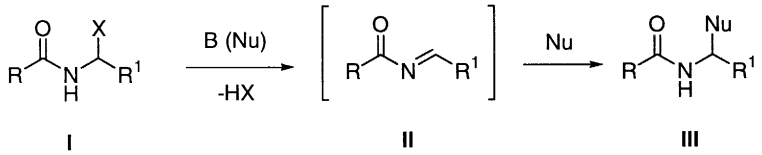
The addition of nucleophilic reagents to unsaturated carbon–nitrogen bonds represents a viable and powerful method to produce an exceptionally wide array of nitrogeneous derivatives.[1] The imino group has gained a particular relevance among these electrophilic substrates as in the case of *N*-tosyl imines that exhibit an enhanced reactivity towards nucleophiles.[2] The preparation of *N*-tosyl imines starting from aromatic aldehydes is rather straightforward, while aliphatic aldehydes are converted to the corresponding imines using *N*-sulfonyl sulfonamides at low temperature.[3] These *N*-tosyl imines must be promptly used since any attempt to isolate them leads to isomerization products.[4] This drawback has stimulated the search for some synthetic analogues of reactive imines that can be easily prepared and which are sufficiently stable. *N*-Acyl-α-substituted amines are a valuable source of *N*-acyl imines since, as portrayed in Scheme 1, a base-(nucleophile)-induced elimination of HX from the amido derivative **I** affords the corresponding imino derivative **II**.



I **II** **III**

Scheme 1.

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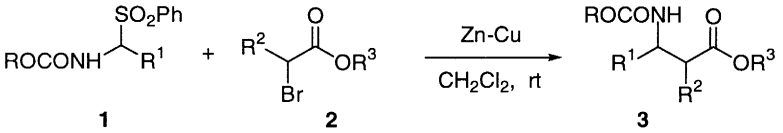
The excess of the nucleophile rapidly attacks the imino derivative **II** as soon as it is formed thus giving the corresponding addition product **III**. Metal ester enolates efficiently add to imino derivatives[5] and amido derivatives of type **I**[6] giving the corresponding β-amino esters and β-lactams.[7] Similarly, zinc enolates generated from the corresponding α-bromo esters[8] may react with *N*-acyl-amines **I** to afford β-amino esters.[9] α-Amidoalkylphenyl sulfones **1** are easily prepared by reaction of a carbamate with a suitable aldehyde and sodium benzenesulfinate in the presence of formic acid.[10] Because of the well known proclivity of the phenylsulfonyl group to act as a good leaving group in elimination reactions,[11] sulfones **1** can behave as *N*-acyl imino equivalents in reactions with nucleophiles.[12] Thus sulfones **1** react with Reformatsky reagents **2** in dichloromethane at room temperature to afford the corresponding β-amino esters **3** in good yields (Scheme 2, Table 1).

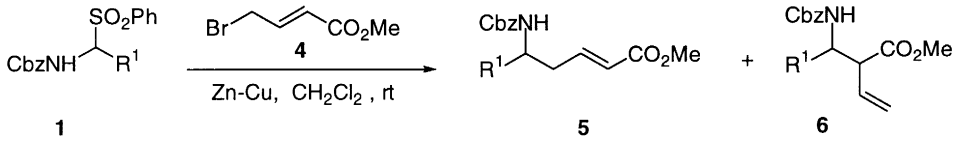


Scheme 2.

Table 1
Reaction of α-amidoalkylphenyl sulfones with Reformatsky reagents

entry		sulfone **1**	α-bromo ester **2**		β-amino ester **3**	
	R	R^1	R^2	R^3	*anti : syn*	yield (%)
a	Bn	Me_2CHCH_2	H	Et	--	75
b	Bn	Me_2CHCH_2	Me	Et	28 : 72	82
c	Bn	Me_2CHCH_2	Me,Me	Me	--	92
d	Et	Me_2CHCH_2	Me	Et	40 : 60	97
e	*t*-Bu	Me_2CHCH_2	Me	Me	40 : 60	76
f	*t*-Bu	$PhCH_2CH_2$	Et	Et	45 : 55	70
g	Bn	$C_5H_{11}CH{=}CHCH_2CH_2$	Me	Me	30 : 70	65
h	Bn	Et	Ph	Et	8 : 92	78
i	*t*-Bu	*c*-C_6H_{11}	Et	Et	25 : 75	79
j	Bn	$Cl(CH_2)_5$	Me	Me	35 : 65	83
k	Bn	$MeO_2C(CH_2)_4$	Me	Et	40 : 60	64

The organozinc reagent is prepared in situ by reaction of the corresponding α-bromo ester with a zinc–copper couple[13] and two equivalents of the reagent are needed in order to get a complete conversion of the substrate. The formation of β-amino esters **3** proceeds with modest to good *syn* selectivity using α-alkyl substituted bromo esters.[14] This trend is opposite to that observed with *N*-acyl-α-methoxy amines which show a preference for the *anti* stereoisomer.[9a] Neither the size of the alkyl substituent of the carbamoyl group, nor the size of the alkyl framework on sulfone **1** seems to have any beneficial effect on the stereoselectivity. The use of *t*-butyl α-bromo esters does not improve the stereochemical outcome of the reaction but leads to a consistent increase of the reaction time (4–18 h) that is usually about 1 h for the entries displayed in Table 1. On the other hand, a satisfactory *syn*:*anti* ratio has been observed using ethyl 2-bromophenyl acetate **2h** thus indicating that α-substitution may be advantageous for the stereoselectivity of the process. Methyl γ-bromocrotonate **4** has been also used for the preparation of the corresponding Reformatsky reagents and the results of its reaction with some sulfones **1** (Scheme 3) are displayed in Table 2.



Scheme 3.

Table 2
Reaction of α-amidoalkylphenyl sulfones with Reformatsky reagent prepared from methyl γ-bromocrotonate

entry	sulfone **1** R^1	**5** : **6**	yield(%)
a	Me_2CHCH_2	68 : 32	88
b	$Cl(CH_2)_5$	60 : 40	80
c	Et	51 : 49	85
d	$MeO_2C(CH_2)_4$	70 : 30	81

The opposite selectivity in favour of the γ- over the α-regioisomer has been observed also in this circumstance using *N*-acyl-α-methoxy amines.[9a] For the α-regioisomer **6** a preference for the *syn* stereoisomer has been once again observed.

In conclusion, α-amidoalkylphenyl sulfones **1** can be profitably used as precursors of the corresponding *N*-acyl imines in reactions with Reformatsky reagents. The β-amino esters are obtained in satisfactory yields with *syn* stereoselectivity.[15] Some extra functional groups such as chlorides, esters and double bonds can be included in the alkyl framework of the sulfones **1** thus extending the synthetic significance of the present methodology.

Acknowledgements

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14. Stereochemical assignments for some compounds **3** have been done by comparison with literature data: Seebach, D.; Abele, S.; Gademann, K.; Guichard, G.; Hintermann, T.; Jaun, B.; Mattews, J. L.; Schreiber, J. V. *Helv. Chim. Acta* **1998**, *81*, 932–982. The chemical shift of the N–H proton for the *syn* isomer is usually around 5.4 ppm while that for the *anti* isomer is around 4.9 ppm.
15. Typical experimental procedure for preparation of β-amino esters **3**. To a stirred solution of sulfone **1** (1 mmol) in dry dichloromethane (5 mL) α-bromo ester **2** (2.1 mmol) was added at room temperature. The zinc–copper couple (0.2 g) was then added and the suspension was strirred for 1 h at room temperature. The solid was filtered and washed with dichloromethane. The combined filtrates were washed with saturated ammonium chloride and then dried over magnesium sulfate. After evaporation of the solvent the crude β-amino ester was purified by column chromatography. **3f**: IR (KBr) ν: 3350, 1716; *syn* isomer: mp 43°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.94 (t, 3H, *J*=7.3 Hz), 1.27 (t, 3H, *J*=7.1 Hz), 1.46 (s, 9H), 1.55–1.80 (m, 4H), 2.40–2.55 (m, 1H), 2.62–2.75 (m, 2H), 3.80–3.95 (m, 1H), 4.15 (q, 2H, *J*=7.1 Hz), 5.35 (d, 1H, *J*=9.9Hz), 7.15–7.31 (m, 5H); *anti* isomer: mp 61°C; ^{1}H NMR δ: 0.89 (t, 3H, *J*=7.3 Hz), 1.24 (t, 3H, *J*=7.1 Hz), 1.46 (s, 9H), 1.60–1.90 (m, 4H), 2.45–2.50 (m, 1H), 2.60–2.80 (m, 2H), 3.75–3.90 (m, 1H), 4.13 (q, 2H, *J*=7.1 Hz), 4.64 (d, 1H, *J*=9.9 Hz), 7.15–7.35 (m, 5H).