Pergamon

Tetrahedron Letters 42 (2001) 1171–1173

TETRAHEDRON
LETTERS

Direct amination of β-oxo esters

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Received 18 September 2000; accepted 29 November 2000

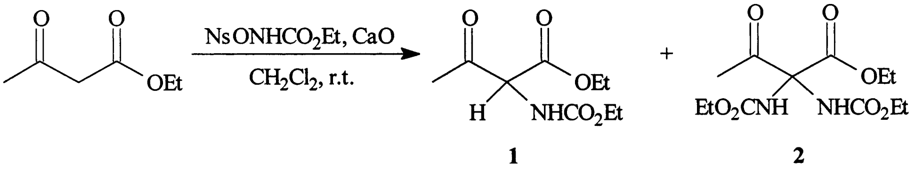
Abstract—The reaction of NsONHCO$_2$Et, in the presence of CaO, with β-oxo esters gives the corresponding aminated products in yields up to 58%. A substrate carrying the Oppolzer sultam undergoes amination with 40% diastereoselectivity. © 2001 Elsevier Science Ltd. All rights reserved.

Among the methods for formation of carbon–nitrogen bonds,[1] the amination of β-dicarbonyl compounds has received little attention.[2–4] An intramolecular reductive amination of β-oxo esters,[5] as well as the addition of dialkyl azodicarboxylates to β-diketones under specialised conditions[6] have been very recently reported.

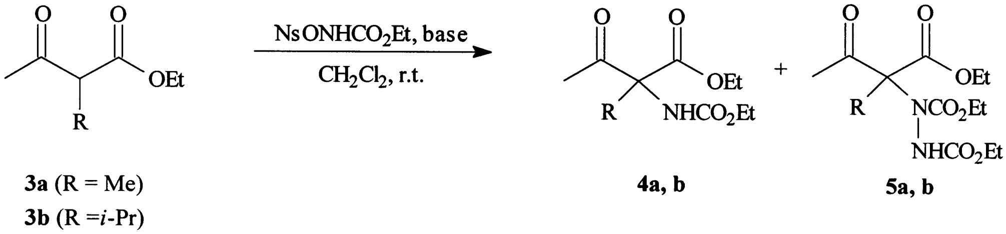
We recently described the use of ethyl *N*-[(4-nitrobenzenesulphonyl)oxy]carbamate (NsONHCO$_2$Et) as an aminating agent for different substrates and for β-enamino esters, in the absence of added bases.[7] Similar reagents have recently reported by Hanessian[8] to give unexpected alkoxyaminocarbonylation of β-dicarbonyl compounds and by others[9] as electrophilic aminating agents on amide cuprates.

We now present our results on the direct amination of β-oxo esters by using NsONHCO$_2$Et slowly added in the presence of inorganic bases. Ethyl acetoacetate can be easily aminated or bis-aminated in the α-position (Scheme 1) at room temperature in dichloromethane solution in 3 h, giving **1**[7] (4%) and **2** (41%) when a threefold excess of CaO was used.

In order to minimise the bis-adduct **2**, an experiment with a fivefold excess of ethyl acetoacetate and a twofold excess of CaO was performed; under these conditions 58% of **1** and 8% of **2** were obtained. In monoalkylated β-oxo esters (**3a**,**b**), under the same conditions, the carbamate or the carbazate functional group can be directly introduced, again in the α-posi-



Scheme 1.



Scheme 2.

Keywords: amination; keto acids and derivatives; amino acids and derivatives; carbamates.

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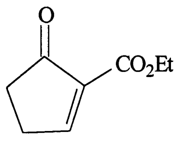
PII: S0040-4039(00)02200-0

tion, giving **4a**,**b** and **5a**,**b** (Scheme 2)[10] and the main product depends on the relative amounts of the reagents used (Table 1).

Interestingly, starting from β-oxo esters having a ring (**3c**,**d**) the bicyclic aziridines[11] **6c**,**d** were isolated (Scheme 3), in addition to products **4c**,**d** and **5c**,**d** (Table 2).

Although no mechanistic interpretation can be made at this point, we believe that hydrogen abstraction by a nitrene can generate small amounts of **7**, that is quickly aziridinated, as proved by the fast reaction of $NsONHCO_2Et$ with an authentic sample of **7**, prepared by a reported procedure.[12]



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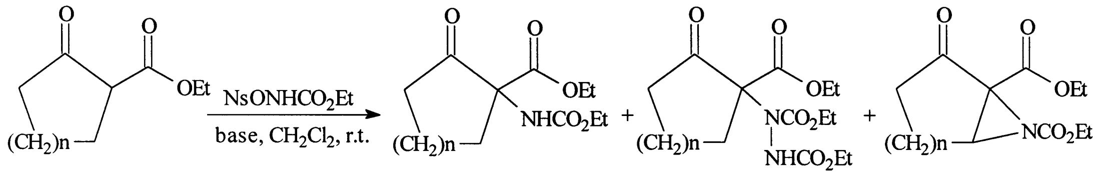
A substrate carrying the Oppolzer sultam **8** underwent amination giving a 54% yield of **9** (Scheme 4) with 40% diastereoselectivity, a value similar to that observed in

Table 1. Amination of monoalkylated β-oxo esters

	Base	Molar ratios substrate:base:$NsONHCO_2Et$	Time (h)	Yields (%)[a]	
				4	**5**
3a	CaO	1:6:2	3	42	22
		5:2:1	1	58	4
		1:6:6[b]	3	14	43
3b	CaO/LiOH	1:6/6:3	5	28	5
		5:2/2:1	1	5	Traces

[a] All compounds were separated by flash-chromatography (hexane/ethyl acetate, 70:30) and characterized by ^{1}H, ^{13}C NMR, IR, GC/MS spectroscopy.

[b] Added in batches.



3c (n=1)
3d (n=2)

4c, d

5c, d

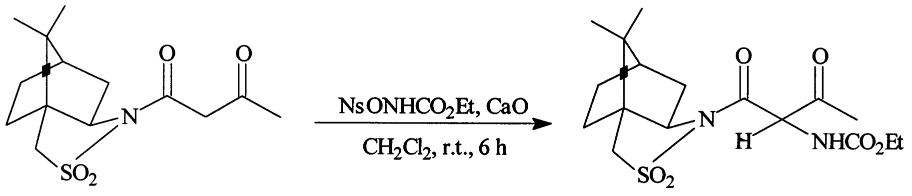
6c, d

Scheme 3.

Table 2. Amination of β-oxo esters **3c**,**d**

	Molar ratios substrate:CaO:$NsONHCO_2Et$	Time (h)	Yields (%)[a]		
			4	**5**	**6**
3c	1:6:2	3	35	4	19
	5:2:1	1	49	–	4
3d	1:6:2	3	38	5	13
	5:2:1	3	40	–	10

[a] All compounds were separated by flash-chromatography (hexane/ethyl acetate, 75:25) and characterized by ^{1}H, ^{13}C NMR, IR, GC/MS spectroscopy.



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9

Scheme 4.

the alkylation of the same substrate.[13] No amination was observed starting from the α-methyl derivative of **8**.

Further experiments aimed at increasing the diastereoselectivity will be reported in due course. The amination of other β-dicarbonyl compounds is also in progress.

Acknowledgements

We thank the Italian Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) and the Università di Roma 'La Sapienza' (National Project 'Stereoselezione in Sintesi Organica. Metodologie e Applicazioni') and Consiglio Nazionale delle Ricerche (CNR) for financial support.

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10. **4a**: IR (CCl_4) 3417, 1749, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12–1.38 (*m*, 6H, CH_2CH_3), 1.72 (*s*, 3H, CH_3), 2.20 (*s*, 3H, CH_3CO), 4.11 (*q*, $J=7.3$ Hz, 2H, OCH_2), 4.24 (*q*, $J=7.3$ Hz, 2H, OCH_2), 6.10–6.35 (*br*, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.04, 14.59, 24.26, 29.78, 61.28, 61.75, 68.63, 154.93, 169.24, 197.48; GC-MS *m/z* 231 (M^+, <1), 189 (21), 188 (65), 158 (27), 143 (28), 142 (33), 116 (40), 115 (32), 114 (19), 88 (54), 86 (33), 70 (26), 44 (13), 43 (41), 42 (100).

    5a: IR (CCl_4) 3391, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15–1.40 (*m*, 9H, CH_2CH_3), 1.63 (*s*, 3H, CH_3), 2.34 (*s*, 3H, CH_3CO), 4.05–4.40 (*m*, 6H, OCH_2), 6.35–6.75 (*br*, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.74, 14.54, 14.89, 19.57, 24.32, 62.22, 63.27, 63.44, 68.72, 156.64, 156.87, 169.16, 199.07; GC-MS *m/z* 318 (M^+, <1), 231 (11), 203 (60), 188 (70), 173 (14), 157 (51), 142 (29), 131 (12), 129 (42), 116 (10), 101 (100), 90 (11), 35 (12), 83 (17), 70 (10), 57 (19), 43 (48), 42 (43).
11. **6c**: IR (CCl_4) 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17–1.38 (*m*, 6H, CH_2CH_3), 1.85–2.55 (*m*, 4H, ring CH_2), 3.60–3.72 (*m*, 1H, CHN), 4.05–4.35 (*m*, 4H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 13.98, 14.12, 19.86, 32.96, 50.60, 51.00, 62.23, 63.35, 157.57, 163.96, 200.46; GC-MS *m/z* 241 (M^+, <1), 125 (26), 124 (13), 123 (100), 97 (10), 96 (11), 95 (67), 68 (16), 67 (29), 42 (11), 41 (17).
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