Reactions with Aziridines; 34[1]. γ-Amidoketones by Amidoethylation of Ketones

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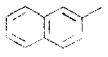
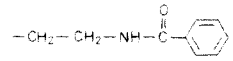
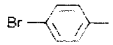
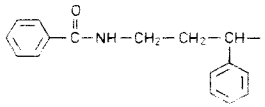
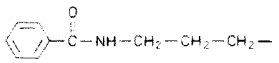
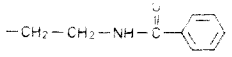
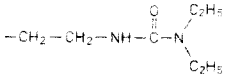
Sodium enolates of ketones react with 1-acyl-, 1-aminocarbonyl-, and 1-alkoxycarbonylaziridines to give γ-amidoketones ([*N*-(4-oxoalkyl)-carboxamides, -ureas, and -carbamic esters]. Twofold amidoethylation in α,α- or α,α'-position can usually be suppressed by using excess enolate, exept for the amidoethylation of 1-indanone.

We have previously reported the *C*-amidoethylation of simple nitriles[2] and esters[2] and of other CH-acidic substrates mostly of the β-dicarbonyl type (see Ref.[2,3] and preceding papers). We now describe the novel *C*-amidoethylation of the enolates of simple ketones **(2)** with *N*-acyl-, *N*-aminocarbonyl-, and *N*-alkoxycarbonylaziridines **(1)**. This reaction represents a one-step syntheses of *N*-(4-oxoalkyl)-carboxamides, *N*-(4-oxoalkyl)-ureas, and alkyl *N*-(4-oxoalkyl)-carbamates, i. e., of γ-amidoketones **(3)**, a hitherto little known class of compounds[4,5]. Compounds **3** may be regarded als protected γ-aminoketones; the amino group can be deprotected after protection or chemical transformation of the ketonic carbonyl group.

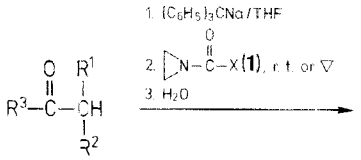
The ketones **2** are deprotonated with tritylsodium in tetrahydrofuran. This deprotonation is most cases indicated by a color change of the red tritylsodium solution. The sodium enolates (usually 100% excess) are subjected to the reaction with the aziridine derivatives **1** in tetrahydrofuran. In some cases, the reaction may not go to completion under the conditions chosen (Table 1) as evidenced by the isolation of benzoic acid in reactions with benzoylaziridine (**1**, X = C_6H_5) due to hydrolysis of **1** during work-up.

Table 1. New Compounds **3**, **4**, **5**, and **7** prepared

Compound	R^1	R^2	R^3	X	Reaction Time[a]	Yield[b] [%]	m.p. [°C]	Molecular Formula[c]
3a	CH_3	CH_3			1 day r.t.	51	84–85°	$C_{19}H_{21}NO_2$ (295.4)
3b	CH_3	CH_3			1 day reflux	52	oil	$C_{17}H_{26}N_2O_2$ (290.4)
3c		$-CH_2-CH_2-$			2 days r.t.	65	98–99°	$C_{19}H_{19}NO_2$ (293.4)
3d		H			4 days r.t.	64	128°	$C_{23}H_{21}NO_2$ (343.4)
3e	CH_3	H			2 days r.t., 3 h reflux	62	oil	$C_{18}H_{19}NO_2$ (281.3)
3f	CH_3	H			1 day reflux	58	oil	$C_{16}H_{24}N_2O_2$ (276.4)
3g	CH_3	H			3 days r.t.	67	61°	$C_{18}H_{18}FNO_2$ (299.3)

3h	H	H			6 days r.t.	44	137°	$C_{21}H_{19}NO_2$ (317.4)
3i	H	H			2 days r.t.[e]	19	169–171°	$C_{17}H_{16}BrNO_2$ (346.2)
4i		H			2 days r.t.[e]	36	144–146°	$C_{26}H_{25}BrN_2O_3$ (493.4)
3j		H			2 days r.t.[e]	51	112°	$C_{24}H_{23}NO_2$ (357.4)
5j		H			2 days r.t.[e]	20	173°	$C_{33}H_{32}N_2O_3$ (504.6)
3k					3 days r.t.[f]	29	116–118°	$C_{24}H_{23}NO_2$ (357.4)
5k					3 days r.t.[f]	5	146–148°	$C_{33}H_{32}N_2O_3$ (504.6)
3l					2 days r.t.	29	oil	$C_{20}H_{23}NO_3$ (325.4)
3m	H				4 h reflux	52	123–125°	$C_{19}H_{19}NO_2$ (293.4)
3n	H				3 days r.t.	37	109–11°	$C_{18}H_{17}NO_2$ (279.3)
4n					3 days r.t.	23	124–126°	$C_{27}H_{26}N_2O_3$ (426.5)
3o	H				4 days r.t.	39	oil	$C_{16}H_{22}N_2O_2$ (274.4)
4o					4 days r.t.	23	oil	$C_{23}H_{36}N_4O_3$ (416.6)
7					1 day r.t.	24[g]	96–98°	$C_{12}H_{12}ClNO_2$ (237.7)

[a] Unless otherwise stated, the ketone enolate was used in 100% excess.
[b] Yield of isolated product. Yields of **3** and **4** or **3** and **5**, respectively, are from the same run.
[c] Satisfactory microanalyses obtained: C ±0.38, H ±0.25, N ±0.32.
[d] The I.R. spectra showed the expected bands (ν); NH: 3250–3390 cm^{-1}; ketone C=O: indanone near 1710 cm^{-1}, other aryl ketones 1670–1690 cm^{-1}, other ketones near 1710 cm^{-1}; urethane (in **3l**): 1720 cm^{-1}; amide I: 1625–1655 cm^{-1}; amide II: 1530–1560 cm^{-1}.
[e] No excess of enolate.
[f] 20% excess of enolate.
[g] Recrystallized from cyclohexane.



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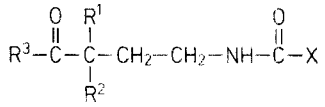

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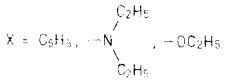
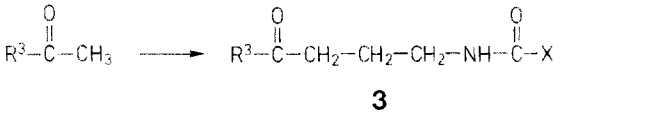


As expected, some twofold amidoethylation may occur. Thus, with methyl ketones α,α-bis[amidoethylation] may predominate even when equimolecular amounts of reaction components are used (e.g., formation of **3i** + **4i**). α,α-Bis[amidoethylation] is also remarkable in the case of 1-indanone (formation of products **3n** + **4n** and **3o** + **4o**) in spite of a 100% excess of enolate whereas it is absent in the case of 1-tetralone. Some α,α′-bis[amidoethylation] to give mixtures of products **3** and **5** is found in the cases of dibenzyl ketone (formation of **3j** + **5j**) and methyl diphenylmethyl ketone (formation of **3k** + **5k**).



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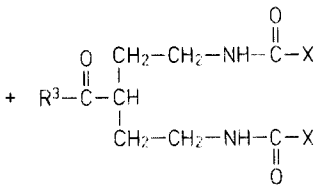

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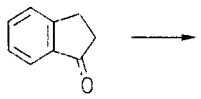
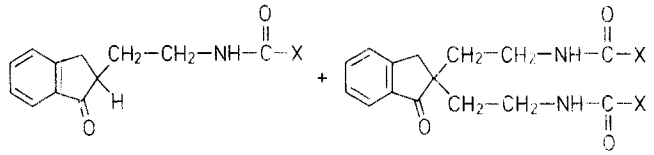
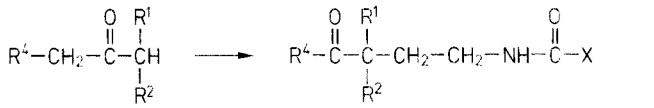




3 **4**



$R^4–CH_2– = R^3$

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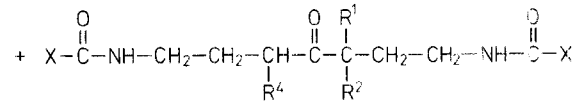

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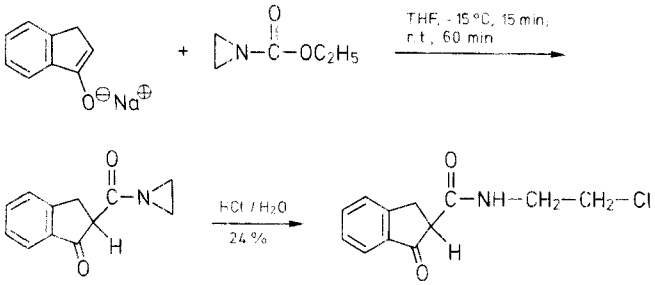
Table 2. ^{1}H-N.M.R.-Spectral Data ($CDCl_3$/TMS_{int}) of Compounds **3**, **4**, **5**, and **7**

Compound	δ [ppm]
3a	1.34 (s, 6H, $2CH_3$); 1.93–2.28 (m, 2H, N—C—CH_2); 3.04–3.53 (m, 2H, N—CH_2); 6.56 (br. s, 1H, NH); 7.21–7.78 (m, 10H_{arom})
3b	1.01 (t, 6H, J = 7.0 Hz); 1.34 (s, 6H, $2CH_3$); 1.88–2.25 (m, 2H, N—C—CH_2); 3.10–3.60 (m, 2H, N—CH_2—C—C—C=O); 3.37 (q, 4H, J = 7.0 Hz, 2N—CH_2); 4.43 (br. s, 1H, NH); 7.30–7.64 (m, 3*m*- and *p*-H_{arom}); 7.64–7.83 (m, 2*o*-H_{arom})
3c	0.70–1.05 (m, 2H, CH—C—CH); 1.05–1.40 (m, 2H, CH—C—CH); 2.06 (t, 2H, J = 6.4 Hz, N—C—CH_2); 3.47 (q, 2H, J = 6.4 Hz, N—CH_2); 6.63 (br. s, 1H, NH); 7.20–7.6 (m, 6*m*- and *p*-H_{arom}); 7.6–7.90 (m, 4*o*-H_{arom})
3d	1.89–2.80 (m, 2H, N—C—CH_2); 3.24–3.70 (m, 2H, N—CH_2); 4.72 (t, 1H, J = 7.0 Hz, CH—C=O); 6.58 (br. t, 1H, J = 6 Hz, NH); 7.05–7.55 (m, 11H_{arom} with s of 5H at 7.30); 7.55–7.83 (m, 2H_{arom}, *o*-H of benzamide); 7.83–8.10 (m, 2H_{arom}, *o*-H of phenyl ketone)
3e	1.23 (d, 3H, J = 7.0 Hz, CH_3); 1.40–2.50 (m, 2H, N—C—CH_2); 3.30–3.83 (m, 3H, N—CH_2—C—CH); 6.80 (br. t, 1H, J = 6 Hz, NH); 7.32–7.60 (m, 6*m*- and *p*-H_{arom}); 7.60–7.84 (m, 2H_{arom}, *o*-H of benzamide); 7.84–8.10 (m, 2H_{arom}, *o*-H of phenyl ketone)
3f	1.06 (t, J = 7.2 Hz, 6H, 2N—C—CH_3); 1.22 (d, 3H, J = 7.0 Hz, CH_3); 1.3–2.4 (m, 2H, N—C—CH_2); 3.21 (q, 4H, J = 7.2 Hz, N—CH_2); 3.3–3.83 (m, 3H, N—CH_2—C—CH); 4.83 (br. t, 1H, J = 5 Hz, NH); 7.37–7.68 (m, 3*m*- and *p*-H_{arom}); 7.85–8.10 (m, 2*o*-H_{arom})
3g	1.18 (d, 3H, J = 7.0 Hz, CH_3); 1.38–2.50 (m, 2H, N—C—CH_2); 3.30–3.83 (m, 3H, N—CH_2—C—CH); 6.63–7.3 (m, 2H_{arom}, CH—CF—CH); 7.3–7.6 (m, 3H_{arom}, *m*-H, *p*-H of benzamide); 7.6–8.23 (m, 4*o*-H_{arom})
3h	2.13 (mc, 2H, N—C—CH_2); 3.25 (t, 2H, J = 7.0 Hz, O=C—CH_2); 3.60 (mc, 2H, N—CH_2); 6.80 (br. s, 1H, NH); 7.27–8.20 (m, 11H_{arom}); 8.48 (br. s, 1H_{arom}, 1-H of naphthyl)
3i	1.83–2.40 (m, 2H, N—C—CH_2); 3.07 (t, 2H, J = 7.0 Hz, O=C—CH_2); 3.57 (q, 2H, J = 6.0 Hz, N—CH_2); 6.73 (br. s, 1H, NH); 7.30–7.60 (m, 3H_{arom}, *m*-H, *p*-H of benzamide); 7.60–7.88 (m, 6H_{arom})
4i	1.66–2.36 (m, 4H, 2N—C—CH_2); 3.20–3.75 (m, 5H, N—CH_2—C—CH); 6.70 (br. s, 2H, 2NH); 7.25–7.6 (m, 6H_{arom}, *m*-H, *p*-H of benzamide); 7.6–7.90 (m, 8H_{arom})
3j	1.60–2.70 (m, 2H, N—C—CH_2); 3.30 (q, 2H, J = 6.4 Hz, N—CH_2); 3.60 (s, 2H, O=C—CH_2); 3.83 (t, 1H, J = 7.2 Hz, O=C—CH); 6.35 (br. t, 1H, J = 6 Hz, NH); 6.7–7.5 (m, 13H_{arom}); 7.53–7.80 (m, 2H_{arom}, *o*-H of benzamide)
5j	1.60–2.60 (m, 4H, 2N—C—CH_2); 2.75–3.54 (m, 4H, 2N—CH_2); 3.72 (t, 2H, J = 7.1 Hz, of *meso* form, CH—CO—CH); 3.94 (dd, J = 5.1/3.7 Hz, 2H of racemic form, CH—CO—CH); 6.30 (br. t, 2H, J = 5.2 Hz, 2NH); 6.50–7.20 (m, 10H_{arom}); 7.20–7.60 (m, 6H_{arom}); 7.62–7.89 (m, 4H_{arom}, *o*-H of benzamide)
3k	2.07 (s, 3H, CH_3); 2.67 (mc, 2H, N—C—CH_2); 3.17 (mc, 2H, N—CH_2); 6.50 (br. t, 1H, J = 5.5 Hz, NH); 7.15–7.53 (m, 13H_{arom} with s of 10H at 7.35); 7.53–7.80 (m, 2H_{arom}, *o*-H of benzamide)
5k	1.68 (mc, 2H, N—C—CH_2—CH_2—C=O); 2.53 (t, 2H, J = 5.6 Hz, O=C—CH_2); 2.70 (mc, 2H, N—C—CH_2); 3.13 (mc, 4H, 2N—CH_2); 6.54 (br. s, 2H, 2NH); 6.91–7.54 (m, 16H_{arom} with s of 10H at 7.28); 7.54–7.82 (m, 4H_{arom}, *o*-H of benzamide)
3l	1.14 (t, 3H, J = 7.0 Hz, CH_3); 2.07 (s, 3H, O=C—CH_3); 2.30–3.16 (m, 4H, N—CH_2—CH_2); 4.07 (q, J = 7.0 Hz, OCH_2); 4.80 (br. t, 1H, J = 5.0 Hz, NH); 7.35 (s, 10H_{arom})

Table 2. (continued)

Compound	δ [ppm]
3m	1.52–2.80 (m, 5H, O=C—CH—CH_2); 2.80–3.15 (m, 2H, Ar—CH_2); 3.60 (mc, 2H, N—CH_2); 6.9 (br. s, 1H, NH); 6.90–7.60 (m, 5H_{arom}); 7.67–8.26 (m, 5H_{arom})
3n	1.78–2.25 (m, 2H, N—C—CH_2); 2.60 (mc, 1H, O=C—CH); 2.96–3.48 (m, 2H, Ar—CH_2); 3.68 (mc, 2H, N—CH_2); 7.10 (br. s, 1H, NH); 7.23–7.94 (m, 9H_{arom})
4n	1.98 (mc, 4H, 2N—C—CH_2); 3.10 (s, 2H, Ar—CH_2); 3.42 (mc, 4H, 2N—CH_2); 7.0 (br. t, 2H, J = 6 Hz, 2NH); 7.20–7.84 (m, 14H_{arom})
3o	1.10 (t, 6H, J = 7.0 Hz, 2CH_3); 1.70–2.18 (m, 2H, N—C—CH_2); 2.48–2.91 (m, 1H, O=C—CH); 3.13–3.68 (m, 8H, Ar—CH_2, N—CH_2—C—C—C=O, 2N—CH_2; with q of 4H at 3.25, J = 7.0 Hz); 4.95 (br. s, 1H, NH); 7.20–7.85 (m, 4H_{arom})
4o	1.04 (t, 12H, J = 7.0 Hz, 4CH_3); 1.90 (t, 4H, J = 7.0 Hz, N—C—CH_2); 2.90–3.65 (m, 14H, Ar—CH_2, 2N—CH_2—C—C—C=O, 4N—CH_2, with s of 2H at 3.20 and q of 8H at 3.20, J = 7 Hz); 4.60 (br. t, 2H, J = 6 Hz, 2NH); 7.20–7.85 (m, 4H_{arom})
7	3.20–3.83 (m, 9H); 7.2 (br. s, 1H, NH); 7.3–7.90 (m, 4H_{arom})

1-Ethoxycarbonylaziridine (**1**, X = OC_2H_5) can be used when the enolate is sufficiently soft in character, e.g., due to aryl substituents in the α-position. Otherwise, carbonyl attack predominates leading to 1-(3-oxoalkanoyl)-aziridines which are easily cleaved during work-up to yield the starting ketone. Thus, the reaction with 1-indanone gives 2-aziridinocarbonyl-1-indanone (**6**) as shown by the isolation of *N*-(2-chloroethyl)-1-oxoindane-2-carboxamide (**7**) upon quenching with dilute hydrochloric acid. After the usual (i.e., non-acidic) work-up, 1-indanone is recovered in 95% yield.



6 **7**

Melting points (uncorrected) were determined with a Reichert melting point microscope. I.R. spectra were recorded on a Perkin Elmer spectrometer type 253 or type 283. ^{1}H-N.M.R. spectra were recorded with a Varian T60 A or with a Bruker HX-90 spectrometer. Tetrahydrofuran was distilled before use after having been refluxed over sodium and potassium until benzophenone gave a blue colour. All reactions were conducted under pure nitrogen. The quality of the nitrogen was controlled by bubbling it through a wash bottle containing a dark green solution of sodium naphtalenide in tetrahydrofuran.

2-[2-(Diethylaminocarbonylamino)-ethyl]-1-indanone (3o) and 2,2-Bis[2-(diethylaminocarbonylamino)-ethyl]-1-indanone (4o); Typical Procedure:

A mixture of naphthalene (2.56 g, 20 mmol), triphenylmethane (4.88 g, 20 mmol), sodium dispersion (50% in mineral oil; 0.92 g, 20 mmol), and tetrahydrofuran (150 ml) is stirred for 3 h. The mixture is then cooled with ice/sodium chloride and a solution of 1-indanone (2.76 g, 20 mmol) in tetrahydrofuran (50 ml) is added dropwise with stirring (decolorization), followed by a solution of 1-(diethylaminocarbonyl)-aziridine (1.43 g, 10 mmol) in tetrahydrofuran (30 ml). The cooling is removed and stirring is continued for 4 days. The solvent is then removed in a rotatory evaporator, and the residue dissolved in dichloromethane (200 ml). This solution is washed neutral with water, then concentrated, and the residue column-chromatographed on silica gel (Merck, 0.06–0.2 mm) using first dichloromethane for removal of the nitrogen-free constituents. Products **3o** and **4o** are eluted with methanol and separated by chromatography on a second column (silica gel as above) using ethyl acetate as eluent to give product **3o** as the first fraction and product **4o** as the second fraction.

In some of the other preparations, the chromatographic separation is performed with mixtures of dichloromethane and ethyl acetate.

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This work is dedicated to Prof. H. Oelschläger on the occasion of his 65th birthday.

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[1] Part 33: Stamm, H., Sommer, A., Woderer, A., Wiesert, W., Mall, T., Assithianakis, P. *J. Org. Chem.*, **1985**, *50*, 4946.

[2] Woderer, A., Assithianakis, P., Wiesert, W., Speth, D., Stamm, H. *Chem. Ber.* **1984**, *117*, 3348.

[3] Stamm, H., Woderer A., Wiesert, W. *Chem. Ber.* **1981**, *114*, 32.

[4] Two compounds of the type **3** have previously been obtained by Schotten-Baumann treatment of 2-phenyl- (or 2-methyl)-pyrroline with benzoyl chloride and aqueous sodium hydroxide: Gabriel, S., Colman, J. *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 513. Gabriel, S. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 1238.