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A ONE-POT SYNTHESIS OF TERTIARY AMINES FROM AMIDES, LACTAMS AND URETHANES

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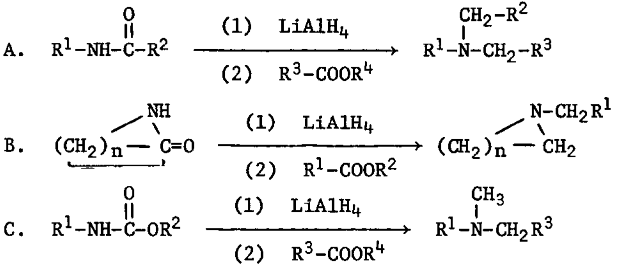
A one-pot synthesis of unsymmetrical tertiary amines from amides, lactams and urethanes has been developed. The reaction is general for all cases examined with the exception of N-aryl containing examples, which are not accessible by this method.

The one-step alkylation of amines by esters in the presence of lithium aluminum hydride has been thoroughly examined,[1] and the use of the same reagent to convert amides and related functionality to amines is well known. We have now combined the synthetic utility of both these processes in a one-step conversion of amides, lactams or urethanes into tertiary amines, according to the sequences A-C (below).



A. $R^1\text{-NH-}\overset{O}{\overset{\|}{C}}\text{-}R^2 \xrightarrow[(2)\ R^3\text{-COOR}^4]{(1)\ LiAlH_4} R^1\text{-}\overset{CH_2\text{-}R^2}{\overset{|}{N}}\text{-CH}_2\text{-}R^3$

C. $R^1\text{-NH-}\overset{O}{\overset{\|}{C}}\text{-OR}^2 \xrightarrow[(2)\ R^3\text{-COOR}^4]{(1)\ LiAlH_4} R^1\text{-}\overset{CH_3}{\overset{|}{N}}\text{-CH}_2R^3$

A related reaction, the one-step conversion of an isothiocyanate to a dimethyl amino compound by lithium aluminum hydride and ethyl formate, has recently been reported.[2]

As a method of synthesis of tertiary amines, especially unsymmetrically substituted examples our procedure is considerably simpler than, and comparable in yield to, the traditional alkylation route. Typical transformations are summarized in the Tables. In all cases, starting materials were prepared by standard procedures.

Table 1. Conversion of amides and lactams R^1NHCOR^2 into tertiary amines $R^1\text{-}\underset{CH_2R^3}{\underset{|}{N}}\text{-CH}_2R^2$

R^1	R^2	Ester ($R^3CO_2R^4$)	Yield[a] [%]
$PhCH_2CH_2$	CH_3	$C_2H_5CO_2C_2H_5$	47
$PhCH_2CH_2$	H	$PhCO_2CH_3$	56
$n\text{-}C_3H_7$	Ph	$C_2H_5CO_2C_2H_5$	55
$(3,4\text{-}OCH_3)Ph\text{-}CH_2CH_2$	H	$C_2H_5CO_2C_2H_5$	32
$-(CH_2)_6-$		$CH_3CO_2C_2H_5$	72
$-(CH_2)_7-$		$CH_3CO_2C_2H_5$	72
$-(CH_2)_{11}-$		$CH_3CO_2C_2H_5$	52

Table 2. Conversion of urethanes $R^1NHCO_2R^2$ into tertiary amines $R^1\text{-}\underset{\displaystyle CH_2R^3}{N}\text{-}CH_3$ (Sequence C).

R^1	R^2	Ester ($R^3CO_2R^4$)	Yield[a] [%]
$PhCH_2$	CH_3	$CH_3CO_2C_2H_5$	47
$PhCH_2$	CH_3	$PhCO_2C_2H_5$	76
$PhCH_2CH_2$	CH_3	$CH_3CO_2C_2H_5$	74
n-C_4H_9	CH_3	$CH_3CO_2C_2H_5$	76
iso-C_4H_9	CH_3	$PhCO_2C_2H_5$	51
n-C_4H_9	C_2H_5	$PhCO_2CH_3$	60
$PhCH_2CH_2$	C_2H_5	$C_2H_5CO_2C_2H_5$	45
$PhCH_2$	C_2H_5	$C_2H_5CO_2C_2H_5$	52

[a] Yields refer to isolated, purified samples. All products were identified by ^1H N.M.R., M.S. and I.R. spectroscopic analysis, and showed physical properties identical with those reported in the literature.

Only typical transformations are reported. The reaction was found to be general for all cases examined, with the exception of phenyl carbamic acid derivatives ($PhNHCO_2R$) which did not yield the desired products. Reactions A-C were carried out by the procedure described below.

A solution of methyl 2-phenylethyl carbamate (2.7 g) in anhydrous ether (50 ml) was added slowly to a solution of lithium aluminum hydride (2.7 g) in anhydrous ether (200 ml). The resulting mixture was stirred and refluxed overnight, and then allowed to cool. It was then decomposed by sequential addition of the following: ethyl acetate (10 ml); water (25 ml); aqueous sodium hydroxide (15% w/v, 100 ml); and water (25 ml). The mixture was then filtered through celite and extracted with ether (3 x 100 ml). The extracts were combined and washed with aqueous hydrochloric acid (5% w/v, 3 x 50 ml). The combined acid wash was basified (conc. ammonia), and extracted with ether (3 x 50 ml). The ether extracts were then combined, dried (sodium sulphate), and evaporated. The residue was then distilled at 105-110°, 15 Torr (Lit.[3] 106°, 15 Torr) to yield ethyl 2-phenylethyl methylamine (1.8 g, 74%), homogeneous by G.L.C. analysis (carbowax 20 MTPA, SE 30). ^1H N.M.R. ($CDCl_3$); $\delta = 1.1$ (t, 3H), 2.2 (s, 3H), 2.4-2.9 (m, 6H), 7.2 (br.s, 5H).

M.S.: m/e (%) = 163 (M^+, 6), 148 (6), 105 (100), 91 (20), 77 (22)

n^D_{22} 1.4970 (lit.[3] n^D 1.4975).

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