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NEW SYNTHETIC "TRICKS" USING OLD REAGENTS. A MILD METHOD FOR THE CONVERSION OF RCONHR' TO RCONHR"

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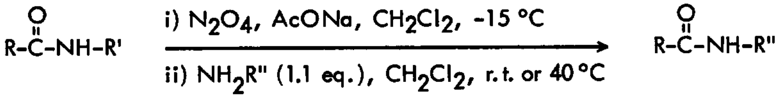
Summary.- N-Alkyl-N-nitrosoamides, RCON(NO)R', react with primary aliphatic amines (NH_2R''), in refluxing dichloromethane or at room temperature, to give RCONHR" in 65-98% yields.

The exchange reaction $RCONHR' + NH_2R'' \rightleftharpoons RCONHR'' + NH_2R'$, sometimes called transamidation[1a] by analogy to the well-known transesterification reactions, has been hardly studied. In principle, the equilibrium could be shifted to the right using more nucleophilic and/or high-boiling NH_2R'', but examples found in the literature are restricted to cases in which starting amides were N-unsubstituted amides, DMF or urea.[1] We wish to report here that the previous transformation of N-alkylamides to the corresponding nitrosoamides facilitates exchange reactions with primary aliphatic amines, in such a way that heating is almost unnecessary:



$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH\text{-}R' \xrightarrow[\text{ii) } NH_2R''\text{ (1.1 eq.), } CH_2Cl_2\text{, r.t. or } 40\,^{\circ}C]{\text{i) } N_2O_4\text{, AcONa, } CH_2Cl_2\text{, } -15\,^{\circ}C} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH\text{-}R''$$

The main results are summarized in the Table (next page). As general comments, we should remark that the reaction takes place in most cases in yields higher than 80%, denitrosation of the N-nitrosoamide[2] by the amine as well as conversion of the N-nitrosoamide to the corresponding ester by rearrangement and nitrogen elimination[3] being in general of little importance.[4] Since the nitrosation of the amides tested was practically quantitative (as shown by TLC and NMR spectroscopy), isolation and purification of the thermally unstable and potentially carcinogenic[5] nitrosoamides can be avoided: after washing the dichloromethane solutions, amines (NH_2R'') may be directly poured into, without taking precautions against moisture; in fact, most experiments with methylamine and ethylamine were carried out in a two-phase system, aqueous solutions of these amines being employed indeed. It is also noteworthy that the replacement of NHR' by NHR" can be done in both senses (e.g., N-butylamides may be converted to N-methylamides, and vice versa).

Work is in progress in order to investigate the reaction of nitrosoamides with secondary and aromatic amines, as well as with amines bearing other functional groups (e.g., amino acids). We are also studying the application of the method to acyl-functionalized or unsaturated amides.

substrate	R"/amine/	product (a)	overall yield (b)	reaction conditions (c)
$CH_3CONH(CH_2)_5CH_3$	methyl	$CH_3CONHCH_3$	85	reflux, 5h/r.t., 48h (d)
$CH_3CONH(CH_2)_5CH_3$	ethyl	$CH_3CONHCH_2CH_3$	80	reflux, 5h
$CH_3(CH_2)_3CONH(CH_2)_3CH_3$	methyl	$CH_3(CH_2)_3CONHCH_3$	65 (e)	reflux, 4h
$CH_3(CH_2)_7CONHCH_3$	ethyl	$CH_3(CH_2)_7CONHCH_2CH_3$	98	r.t., 5 h
$CH_3(CH_2)_7CONHCH_3$	benzyl	$CH_3(CH_2)_7CONHCH_2Ph$	88 (f)	reflux, week-end
$CH_3(CH_2)_7CONHCH_3$	cyclopropyl	$CH_3(CH_2)_7CONHC_3H_5$	92 (f)	reflux, week-end
$CH_3(CH_2)_7CONH(CH_2)_3CH_3$	methyl	$CH_3(CH_2)_7CONHCH_3$	98 (g)	reflux, 4h
$CH_3(CH_2)_7CONH(CH_2)_3CH_3$	ethyl	$CH_3(CH_2)_7CONHCH_2CH_3$	95 (g)	r.t., 60h/reflux, 5h
$PhCONHCH_3$	ethyl	$PhCONHCH_2CH_3$	86	reflux, 1 h
$PhCONHCH_3$	butyl	$PhCONH(CH_2)_3CH_3$	84 (h)	reflux, 5h
$PhCONHCH_3$	benzyl	$PhCONHCH_2Ph$	84 (h)	reflux, week-end
$PhCONHCH_3$	cyclohexyl	$PhCONHC_6H_{11}$	68 (h)	reflux, week-end

(a) Structures were confirmed by ^{1}H NMR and IR spectroscopy, and by chromatographic comparison with authentic samples. By-products arising from N(NO)R' moieties (i.e., diazoalkanes, alcohols, and so on) were not trapped nor determined. (b) Yields have not been optimized. (c) General procedure.- Anh. sodium acetate (3.1 g) was added to a stirred soln of the amide (1.0 g) in 200 ml of dichloromethane cooled to -15°C. A stream of nitrogen dioxide was bubbled through the suspension until TLC indicates that the amide was completely reacted (<1 h). The mixture was then washed with aq. sodium hydrogencarbonate and water. Amine (1.1 eq.) was added and the flask maintained at r.t. or heated to reflux. When the nitrosoamide disappeared (TLC), the mixture was washed with 2N hydrochloric acid, dried over anh. sodium sulphate, and the solvent and volatile by-products removed in vacuo. (Impurities such as esters, when obtained, may be easily eliminated by saponification. Separation of water-soluble amides was accomplished by evaporation of the reaction mixture to dryness, extraction with water, washing with a small volume of ether, and elimination of water in vacuo.)
(d) Yields at r.t. were slightly lower. (e) About 15% of substrate (denitrosated product) was recovered.
(f) Methyl nonanoate was obtained in ca. 5% yield. (g) Small amounts ($\leq$1%) of denitrosated product and butyl nonanoate were detected by GC. (h) Methyl benzoate (5-15%) was also obtained.

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