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NEW SYNTHETIC "TRICKS". FROM ALIPHATIC AMINES AND AMIDES TO AZIDES AND/OR HOW TO CONVERT RNHCOR' INTO RNHCOR" AVOIDING DRASTIC HYDROLYSES

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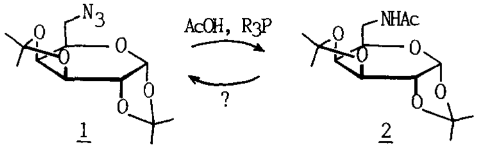
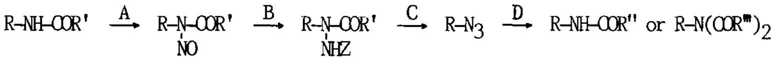
Controlled reduction of N-alkyl-N-nitrosoamides to hydrazides followed by nitrosation and fragmentation affords azides in 80% overall yields, under mild conditions. This simple idea is the basis of methods for the conversion of alkylamines and N-alkylamides to alkyl azides, of RNHCOR' into RNHCOR" or RN(COR‴)$_2$, and of lactames into ω-azido esters or ω-azido acids.

Transformation of RNH_2 into RN_3, the reverse process of the widely utilized reduction of azides to amines, has been occasionally investigated, with several purposes (although mainly aimed at protecting the basic/nucleophilic/reducing amino group) and with variable success.[1-5] Also, in connection with other studies in which we developed a one-pot reaction for the conversion of azides to amides (e.g., 1 → 2),[6] we had thought to recycle some amides to azides for saving starting material.



We report here that these two synthetic problems (and two other commented below) may be closely related and solved by means of the following general strategy which introduces the additional nitrogen atoms step by step but more confidently, generally in better overall yields.



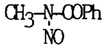
$$\text{R-NH-COR}' \xrightarrow{A} \underset{\text{NO}}{\text{R-N-COR}'} \xrightarrow{B} \underset{\text{NHZ}}{\text{R-N-COR}'} \xrightarrow{C} \text{R-N}_3 \xrightarrow{D} \text{R-NH-COR}'' \text{ or R-N(COR}''')_2$$

Z=H or Ac

According to this scheme, RNHCOR' (and obviously RNH_2) could be converted into RN_3,[7] RNHCOR' could be changed to RNHCOR"[8] or RN(COR‴)$_2$ avoiding previous drastic hydrolyses of RNHCOR' to RNH_2, and N-alkylhydrazides (and N-alkylhydrazines) could be prepared from amides (or amines). Furthermore, when R and R' are linked (i.e. in lactames) the cleavage of the N-COR' bond could give rise to ω-azido acids or ω-azido esters. Since the nitrosation of most amides (step A) can be performed quantitatively in cold, under anhydrous conditions,[9,10] and since step D has been already disclosed,[6] only the reduction step (B) and the nitrosation-fragmentation step (C) are emphasized here.

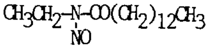
Reduction of Nitrosoamides to Hydrazides

We have systematically investigated the reduction of N-nitrosoamides 3-8 to their N-amino derivatives under the following conditions: (a) $SnCl_2/HCl,Et_2O$/r.t.; (b) $Sn(OAc)_2/AcOH$/r.t.; (c) Sn/aq HCl,EtOH/r.t.; (d) Zn/AcOH/r.t.; (e) $Zn/NH_4OH,NH_4Cl,EtOH/0°C$; (f) H_2/Pd-C/MeOH/r.t.; (g) H_2/Pd-C/AcOH/r.t.; (h) Al-Hg/aq Et_2O/r.t.; (i) Al-Hg/aq Et_2O/AcOH/r.t.; (j) $TiCl_3/NaAcO/H_2O$,MeOH/r.t.; and (k) $TiCl_4/Mg/CH_2Cl_2,Et_2O/0°C$.



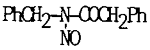
$$\underset{\text{NO}}{\text{CH}_3\text{-N-COPh}}$$

3



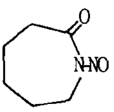
$$\underset{\text{NO}}{\text{CH}_3\text{CH}_2\text{-N-CO(CH}_2)_{12}\text{CH}_3}$$

4



$$\underset{\text{NO}}{\text{PhCH}_2\text{-N-COCH}_2\text{Ph}}$$

5



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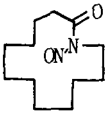

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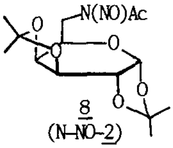
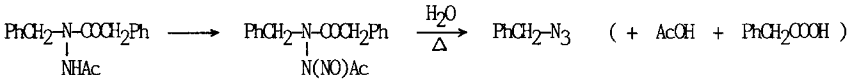


8 (N-NO-2)

The best results have been obtained with Zn/AcOH (80-85% of pure hydrazides[11] were isolated after adding dropwise solutions of 3-8 into a suspension of Zn in AcOH maintained at 10-15°C) and with $TiCl_4$/Mg (ca. 60% yields). Under the remaining conditions, the yields of RN(NH_2)COR' have always been below 10%, the corresponding amides being the predominant products.

Nitrosation of N-Alkylhydrazides and Cleavage

Although the nitrosation of unsubstituted hydrazides is known to afford acyl azides since 1898,[12] the reactivity of RCO-NR-NH_2 and RCO-NR-NH-COR with nitrosating agents has not been reported, to our knowledge. Using RN(NHAc)COR', performing the nitrosation in CH_2Cl_2 with N_2O_4 in cold,[9,10] and treating the nitrosated product with NH_4OH in cold or heating it in MeOH or in H_2O/THF for a few hours, azides were obtained in 70-75% yields in all cases. For instance:



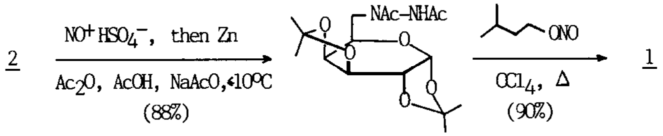
$$PhCH_2\text{-}\underset{NHAc}{\underset{|}{N}}\text{-}COCH_2Ph \longrightarrow PhCH_2\text{-}\underset{N(NO)Ac}{\underset{|}{N}}\text{-}COCH_2Ph \xrightarrow[\Delta]{H_2O} PhCH_2\text{-}N_3 \quad (+\ AcOH\ +\ PhCH_2COOH\ )$$

The reaction can also be accomplished by nitrosation of the non-acetylated hydrazides, i.e. R-N(NH_2)-COR', with $NaNO_2$/AcOH, though in more variable yields (45-85% of azide).

Optimized Procedure

The best way we have found to shorten or simplify.the experimental procedure is to perform the first nitrosation (A) and the reduction (B) as a one-pot reaction and to carry out the second nitrosation and the cleavage at the same time, as follows:

One mmol of the amide and ca. 400 mg of NaAcO in 3 ml of Ac_2O and 3 ml of AcOH were treated at 0-10ºC with 250 mg of $NO^+HSO_4^-$; when the nitrosation was complete (TLC), urea and then a cold suspension of Zn powder in AcOH were added; almost immediately the mixture was filtered, the solution was concentrated under vacuum, and the residue was purified by chromatography to afford the diacylhydrazine. This compound (0.8 mmols), isopentyl nitrite (ca. 8 mmols), and 5-10 ml of CCl_4 were heated at reflux overnight; elimination of the solvent and excess of isopentyl nitrite and purification of the residue on silica gel gave the azide. Thus, 2 was transformed to 1 in good yield (88%x90%):



In similar overall yields (ca. 80%) $PhCH_2NHCOCH_2Ph$ was converted into $PhCH_2N_3$, caprolactame afforded $N_3(CH_2)_5COOC_5H_{11}$, and dodecanolactame gave $N_3(CH_2)_{11}COOC_5H_{11}$. For the conversion of RNH_2 to RN_3, the acetylation of the amine in situ, by the "solvent" itself (Ac_2O, AcOH, NaAcO), is obviously recommended.

References and Footnotes

1) Yields between 23% and 47% are obtained from RNHMgX and TsN_3, according to $RNH^{\ominus}+TsN_3 \rightarrow RN_3+TsNH^{\ominus}$ (W.Fischer,J.P. Anselme,JACS-89,5284,1967; J.B.Hendrickson,W.A.Wolf,JOC-33,3610,1968; J.P.Anselme,W.Fischer,T-25,855,1969).

2) Analogous diazo-transfer reactions, using RNH_2 and triflyl azide, proceed in 19-78% yields (C.J.Cavender,V.J. Shiner,JOC-37,3567,1972; J.Zaloom,D.C.Roberts,JOC-46,5173,1981).

3) The reaction of cyclohexylamine plus methyllithium with N_2O under pressure only gives a 15% yield of cyclohexyl azide (G.Koga,J.P.Anselme,JCS-CC,446,1968).

4) Treatment of RNH_2 with organic hyponitrites did not give RN_3 at all (F.Urpí,Grad.Thesis,Univ.Barcelona,1981).

5) For other approaches to alkyl azides from alkylamines see: (a) A.R.Katritzky et al.,JCS-PTI,849,1980; (b) P.J. DeChristopher et al.,JACS-91,2384,1969; J.B.Hendrickson et al.,JACS-95,3412,1973.

6) J.Garcia,F.Urpí,J.Vilarrasa,TL-25,4841,1984; J.Garcia,J.Vilarrasa,X.Bordas,A.Banaszek,TL-27,639,1986; J.Garcia, Doct.Thesis,Univ.Barcelona,1986.

7) Albeit longer, it could be an alternative route to the above-mentioned diazo-transfer reactions for molecules including functional groups or unsaturations incompatible with TfN_3 or Tf_2O^2 or with TsN_3 or basic media.

8) This is the complement of an earlier process[9] in which the amine moiety of amides with "valuable" acyl groups is replaced by another amine: $R_{\$}CONHR' \rightarrow R_{\$}CON(NO)R' \rightarrow R_{\$}CONHR''$. ("Valuable" means here with some functions, **chiral** centers, or protecting groups sensitive to acids, bases, or heating.) In the present paper the alternative possibility is developed: $R'CONHR_{\$} \rightarrow\rightarrow N_3R_{\$} \rightarrow R''CONHR_{\$}$.

9) J.Garcia,J.Vilarrasa,TL-23,1127,1982; J.Garcia,J.González,R.Segura,F.Urpí,J.Vilarrasa,JOC-49,3322,1984.

10) E.H.White,JACS-77,6008,1955.

11) Either hydrazides RN(NH_2)COR' or RN(NHAc)COR' may be obtained at will: if the excess of AcOH is eliminated at r.t. (vacuum pump), the free N-aminocarboxamide can be isolated; on the other hand, if AcOH is eliminated at 40-50ºC of if the reduction is performed in the presence of Ac_2O (i.e. with Zn/AcOH/Ac_2O), the diacylhydrazine is directly obtained.

12) cf. "Methoden der Organischen Chemie (Houben-Weyl)",Band 8,p.681,G.Thieme Verlag,Stuttgart,1952.

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