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NEW CHEMISTRY OF DIAZOESTERS FROM THERMAL REARRANGEMENT OF N-ALKYL-N-NITROSOAMIDES

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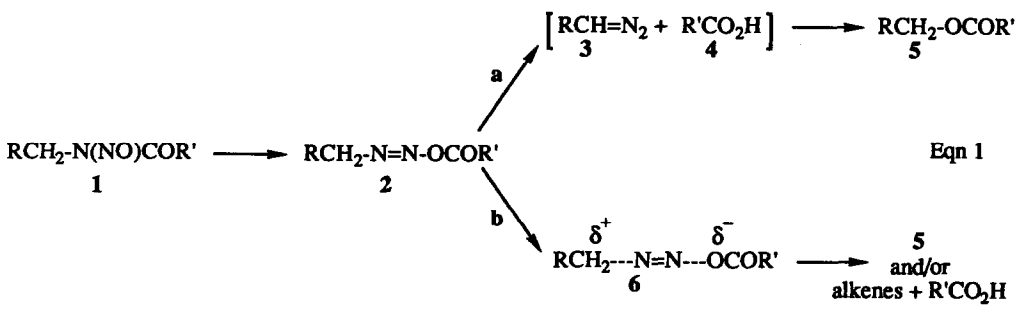
Abstract -- New chemistry is observed in the thermal rearrangement of N-alkyl-N-nitrosoamides **1** under highly nucleophilic, dissociating conditions. An apparent change in the mechanism of the rate-determining step is noted. In DMSO containing N-methylmorpholine-N-oxide, oxidative deamination of **10** via **11** and **12** (Eqn 3) to aldehydes occurs in good yield.

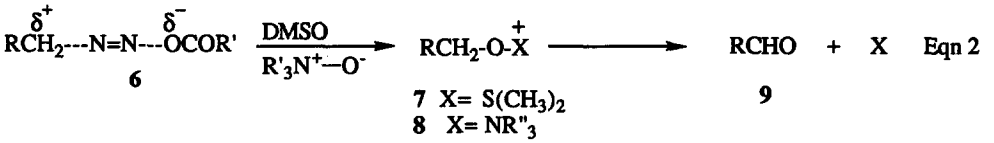
The thermal decomposition of N-alkyl-N-nitrosoamides **1** has been studied in detail over the past forty years.[1] The conversion of **1** to carboxylic esters **5**[2,3] proceeds best in nonpolar solvents via breakdown of transient diazoesters **2** to diazoalkanes **3** and carboxylic acids **4** (Eqn 1, path **a**).[4] Subsequent recombination of **3** with **4** forms **5**. This ester synthesis was recently improved[5] and several new methods for preparing alkenes, alkynes, enol acetates and phosphotriesters from amines were reported based on the facile generation of diazoalkanes from **2**.[6,7]

However direct nucleophilic substitutions on **2** via **6** (Eqn 1, path **b**) have been less well studied,[2,8,9] in part because dissociative elimination of N_2 from **2** is a complex reaction whose stereochemistry (intramolecular retention, intramolecular inversion or intermolecular inversion) is strongly influenced by solvent.[8,9] Added nucleophiles have relatively little effect, suggesting that S_N reactions play a minor role in the overall chemistry of **2**.



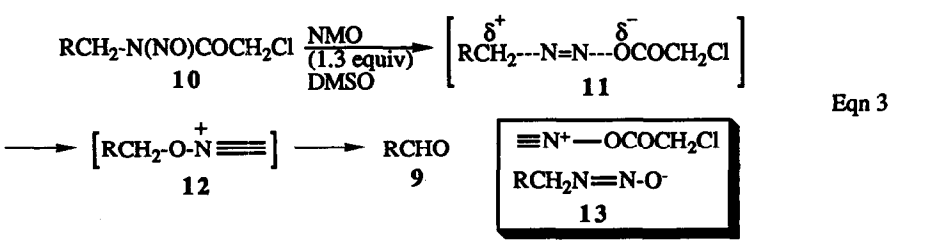
Eqn 1

We reasoned that a strongly nucleophilic tertiary amine oxide (typically μ=4.3-5.0 D)[10] might promote substitution by expelling a favorable leaving group ($R'CO_2^-$) in **6** with the assistance of a dipolar aprotic solvent like dimethyl sulfoxide (DMSO). Such a combination might also suppress internal return leading to **5** and at the same time present two ways to intercept **6** under oxidative conditions (Eqn 2). Fragmentation of either onium salt **7** or **8** ought to furnish aldehydes.[11]



In preliminary experiments with DMSO alone, N-(*n*-decyl)-N-nitrosoacetamide rearranged at 70°C to decanal and decyl acetate in a 1:5 ratio. Superior results were obtained with chloronitrosoamide **10** (cf. Eqn 3, R=C_9H_{19}) where a 2:3 ratio of aldehyde:ester at 55°C was observed, consistent with the better leaving group in **11**. Unfortunately the unstable nitroso*dichloro*acetamide slowly formed ester below rt.[5] The corresponding *o*-difluorobenzamide afforded 1:1 aldehyde:ester, but required 70°C. In each instance, significant amounts of 1-decene were also produced.

When anhydrous N-methylmorpholine-N-oxide (NMO, 1.3 equiv) was added to a d_6-DMSO solution of N-decyl-N-nitroso-α-chloroacetamide (**10**, Eqn 3) at rt, nitrogen was rapidly evolved and **10** was consumed within 2 h, as judged by NMR. The methyl resonance for NMO at 3.0 ppm gave way to a new singlet at 3.4 ppm, corresponding to oxyammonium salt **12**. A singlet for N-methylmorpholine gradually appeared at 2.2 ppm and decanal (50%) was obtained after 41 h at rt, along with the corresponding aldol dimer (3-6%), 1-decene (24%) and minor amounts of other decenes. Only traces of decyl α-chloroacetate were detected. Aldehyde formation was much faster in the presence of triethylamine (1 equiv, 3 h, rt), which promoted the fragmentation of **12**.[12] Other primary alkylamines could also be oxidized [veratrylamine to veratraldehyde (64%); hydrocinnamylamine to hydrocinnamaldehyde (49%)].



Two mechanistic features about this reaction were especially noteworthy. First, *the rapid evolution of N_2 meant that amine oxide strongly promoted the initial rearrangement of 10 to 11.* This finding contrasts with the classic studies of Hey[13] and Huisgen[14] in which acyl migration exhibited first order kinetics, and dissociative processes over a range of nonpolar to polar, protic solvents were ruled out. Furthermore the absence of crossover products, solvent, salt and substituent effects indicated that diazoester formation involved a concerted acyl migration. In the present experiments, DMSO probably facilitated nucleophilic attack at the nitrosoamide carbonyl by NMO, thus promoting acyl migration from **10** to **11** via transient ion pair **13** (Eqn 3). Although in principle a catalytic process, consumption of NMO by **11** in product-forming reactions kept turnover numbers low (typically 0.15 equiv NMO led to 25-30% consumption of **10**).

Secondly, *the combination of NMO in DMSO completely suppressed ester formation during the rearrangement of 10.* Several observations indicated that nucleophilic attack by NMO on diazoester **11** was the predominant mode of decomposition in these reactions.[15] First, controls established that no decanal was formed in the reaction of authentic 1-diazodecane with NMO-DMSO, thus eliminating path **a** (Eqn 1) as the source of aldehyde.[16] Moreover the yield of decanal was higher with NMO-DMSO (50% from **10**) than with DMSO alone (30%), and higher still (60%) in mixtures of NMO-DMSO containing 0.1*M* $LiClO_4$, as would be expected for a dissociative process. Finally, an independent synthesis of **11** by O-acylation of potassium *n*-decanediazotate ($C_{10}H_{21}$-N=N-O$^-K^+$)[17] with chloroacetyl chloride in NMO-DMSO also furnished decanal as the major product.

In summary the thermal rearrangement of N-alkyl-N-nitrosoamides can be dramatically redirected under highly nucleophilic, dissociating conditions with an apparent change in mechanism of the rate-determining step. Moreover the enhanced electrophilic character of intermediate diazoesters like **11** can be used to achieve the overall oxidative deamination of parent amines.

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15. 1-Decene is thought to arise by the NMO-induced E_2 elimination of **11**, since similar eliminations are observed in the reaction of alkyl halides with NMO-DMSO (A. Godfrey, unpublished).
16. Aldehyde formation by direct S_N2 attack of NMO on the starting nitrosoamide **10** was also ruled out using N-decyl-N-nitroso-*o*-dichlorobenzamide, which does not rearrange to **2**, even at 100°C.
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