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A New Mode of Reactivity of N-Methoxy-N-methylamides with Strongly Basic Reagents

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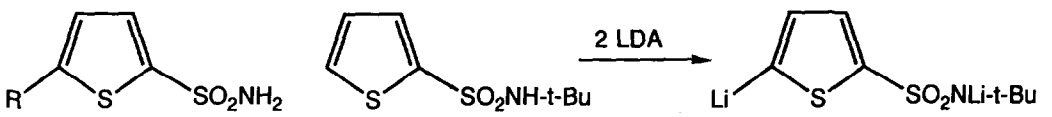
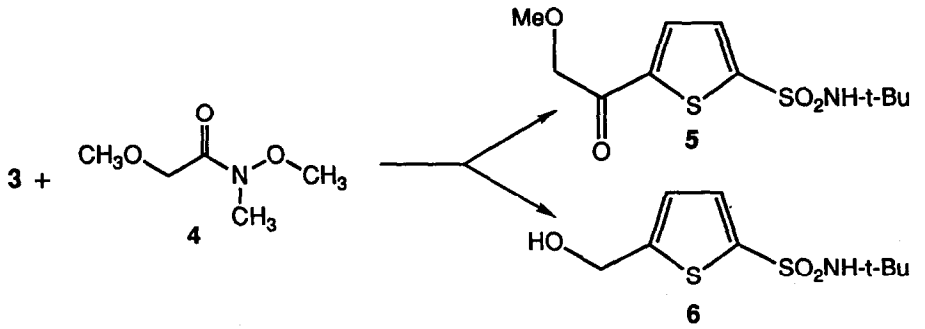
Abstract In applying N-methoxy-N-methylamides as acylating agents for carbanions, an unusual mode of reactivity was discovered. In particular, competitive transfer of a hydroxymethyl group was observed. The mechanism of this reaction is described, and involves a base induced E2 elimination of the N-methoxy-N-methylamide generating formaldehyde and the corresponding N-methylamide anion.

The reaction of carbanions with N-methoxy-N-methylamides (the Weinreb ketone synthesis[1]) and other N-alkoxy-N-alkyl amides (e.g., N-acylisoxazolidides[2]) is a convenient intermediate step in the conversion of carboxylic acids to ketones. In our search for carbonic anhydrase inhibitors for ophthalmic use,[3] we have employed this reaction for the construction of 5-acylthiophene-2-sulfonamides (**1**, R = acyl) from N-*t*-butylthiophene-2-sulfonamide **2** via the N,5-dilithiothiophene sulfonamide **3** and subsequent cleavage of the *t*-butyl protecting group.[4] In this paper we report an unusual side-reaction that occurred between **3** and (N-methyl-N-methoxy)methoxyacetamide **4** which led to the formation of a hydroxymethylated derivative **6**. Since this reaction represents a potential limitation on this strategy for ketone synthesis, we report also an investigation of the mechanism of this transformation.



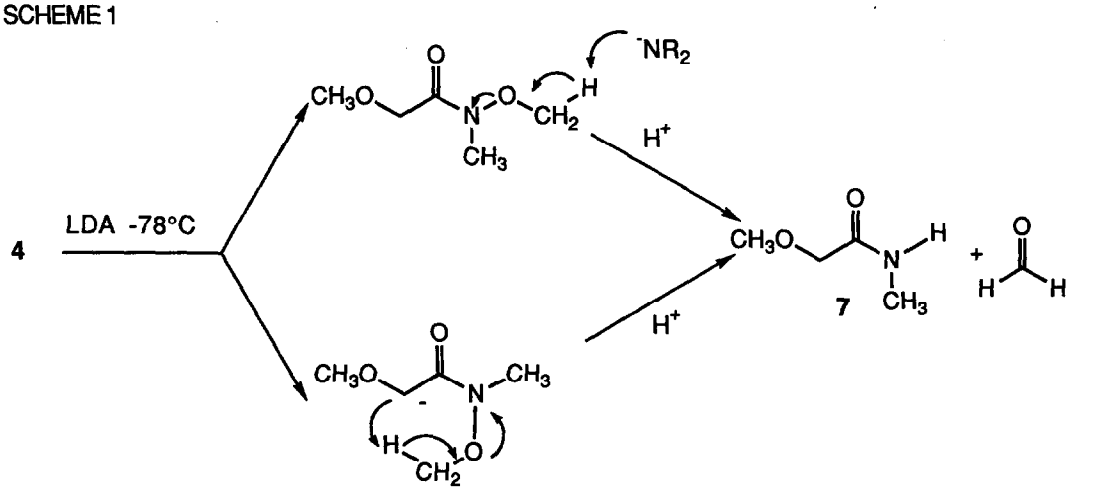
1 **2** **3**

Treatment of **2** with 2.1 eq of lithium diisopropyl amide (LDA) at -78°C in THF gave N,5-dilithiothiophene sulfonamide **3**. N-methoxy-N-methylamide **4** was added at the same temperature. The mixture was warmed to 0°C and quenched with dilute HCl. The ^{1}H NMR spectrum of the crude product showed three thiophene-containing materials present in a ratio of 66:18:16. The least abundant component of the mixture was unreacted starting material. The major product was the expected ketone **5**, which was isolated in 49% yield following chromatography and recrystallization. The ^{1}H NMR spectrum of the second product (isolated in 15% yield) was characteristic of a 2,5-disubstituted thiophene. However, the resonances for the aromatic protons were observed at significantly higher field than the aromatic protons in **5**. In addition, the proton in the 4-position of the thiophene was a doublet of triplets (J=1.0 and 3.7 Hz) suggesting that the 5-position bore a methylene substituent. The only structure in accord with the ^{1}H NMR spectrum and combustion analysis was the 5-hydroxymethylated compound **6**. *Thus it appeared that the acyl transfer reagent also was capable of serving as a source of formaldehyde.*



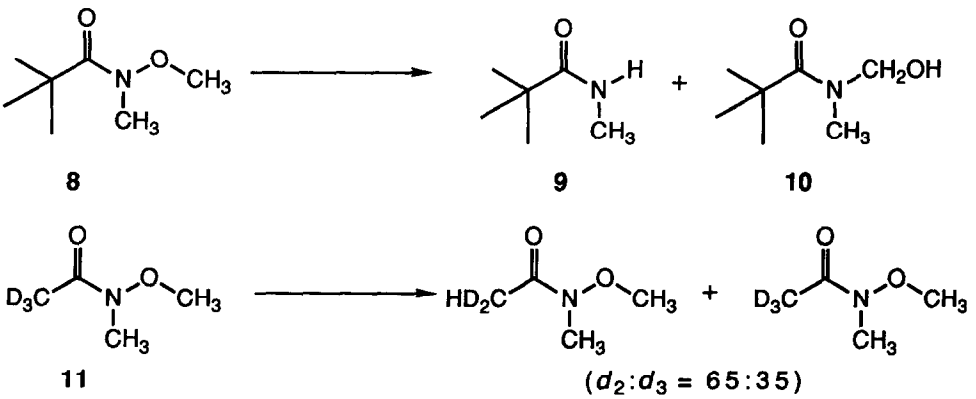
To understand better the fate of **4** under the reaction conditions, **4** was exposed to LDA (1 eq, -78°C, 45 min). The mixture was quenched at the same temperature by the addition of methanol. Isolated from this experiment were a small amount of unreacted **4** and the secondary amide **7**. In fact, a subsequent experiment showed that the formation of **7** proceeded to the extent of 73% within 5 min at -78°C! Thus it appears that in the presence of a hindered, strongly basic reagent, this N-methoxy-N-methylamide decomposes, generating the amide anion and formaldehyde. To our knowledge this is an unprecedented mode of decomposition of an N-alkoxy amide.[5]

SCHEME 1



Three mechanistic possibilities were considered to account for the observed reaction. One of those was the transient formation of an alkoxymethyl carbanion, perhaps stabilized by the proximal amide group, followed by elimination of the amide anion. However, the rapidity with which the decomposition occurred at -78°C indicated that if such an intermediate formed, it is extremely short-lived. No evidence for its formation could be obtained by quenching the reaction mixture at early time points with MeOD. The remaining mechanistic possibilities are shown in Scheme 1. The first (and simplest) mechanism is a direct bimolecular elimination (E2) reaction. However, it also

was clear that enolate formation could occur rapidly under the reaction conditions and that decomposition via unimolecular decomposition of the enolate was possible. Two experiments were devised to test these possibilities. In the first, the N-methoxy-N-methylamide (**8**) of pivalic acid was prepared and subjected to the conditions described for the decomposition of **4** with the exception of quenching the reaction with HOAc rather than methanol. Two products, the secondary amide **9** and the corresponding methylol derivative **10** were obtained. Both obviously were derived from the decomposition of the amide and the generation of formaldehyde by the E2 elimination mechanism. In the second experiment the N-methoxy-N-methylamide **11** derived from d_3-acetic acid was prepared and exposed to LDA. Surprisingly, no evidence for the formation of N-methyl acetamide could be obtained! Instead the starting amide was recovered. The ^{1}H NMR of the recovered amide showed that it was a 65:35 mixture of d_2 and d_3 species.[6] Clearly the acetamide enolate had formed in this case, but it was inert to further transformation. In summary, the mechanism of formaldehyde formation is the E2 elimination.



It is interesting to note that the yield of the hydroxymethylated thiophene **6** is approximately equal to the excess of LDA employed in generating the thiophene dianion. Indeed, when n-butyllithium was employed to generate a dianion from **2** no evidence for hydroxymethylation was found. (However, the choice of base has a profound effect on the regiochemistry of the acylation reaction.[4] The major product in that case is the 3-acylthiophene sulfonamide.) Thus, it is our belief that the phenomenon described here is unique to those situations where one attempts to react an N-methoxy-N-methyl amide either with, or in the presence of, a sterically demanding base. Furthermore, the decomposition of these amides is also sensitive to the details of their own structure. In systems which present no steric encumbrance to enolate formation, the E2 elimination reaction may be suppressed entirely by enolization.

In conclusion, we have documented a novel mode of reactivity of N-methoxy-N-methylamides. These observations complement those reported recently by Rapoport[7] on new modes of decomposition of N-acyl isoxazolidides, which also have been of great utility as reagents for the transfer of acyl groups to carbanions.[2] It is particularly interesting that the decomposition pathways for the two classes of reagents are entirely different. Together, these results provide a significant caveat in the application of N-alkoxy amides to the synthesis of ketones

from carboxylic acids.

Experimental. A solution of 6.7 mL (48 mmol) diisopropyl amine in 30 mL dry THF (Fisher anhydrous grade) was cooled to -78°C under an atmosphere of nitrogen. n-Butyllithium (30 mL, 1.6M solution in hexane, 48 mmol) was added dropwise and the resulting solution of LDA was stirred for 10 min. A solution of 5.0 g (23 mmol) of **2** in 30 mL THF was added dropwise and the resulting suspension was stirred for 45 min at -78°C. To this mixture was added 3.0 g of **4** (23 mmol) dissolved in 10 mL THF. The cooling bath was removed and the mixture was allowed to warm to 0°C and to stir at that temperature for 30 min. The reaction mixture was poured into dilute HCl and brine. The organic phase was separated, dried and evaporated in vacuo to give 6.9 g of an oil which was chromatagraphed on silica gel (0-4% MeOH/$CHCl_3$). The major product was recrystallized from CCl_4 affording 3.25 g (49 %) of **5**: ^1H NMR ($CDCl_3$) d 7.78 (1H, d, J=3.9Hz), 7.62 (1H, d, J = 3.9Hz), 5.50 (1H, br s), 4.52 (2H, s), 3.52 (3H, s), 1.32 (9H, s). The minor product was further purified by chromatography on silica gel (20% EtOAc/ hexane) to give 0.90 g (15 %) of **6**, mp 74-78°C: ^1H NMR ($CDCl_3$) d 7.46 (1 H, d, J =3.8Hz), 6.90 (1H, d of t, J = 3.7,1.0Hz), 4.85 (2H, br d, J = 4.9), 4.75 (1H, s), 2.38 (1H, m), 1.29 (9H, s). Anal. Calcd for $C_9H_{15}NO_3S_2$: C, 43.35; H, 6.06; N, 5.62. Found: C, 43.61; H, 6.31; N, 5.64.

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