N,N'-Dimethoxy-N,N'-Dimethylethanediamide: A Useful α-Oxo-N-Methoxy-N-Methylamide and 1,2-Diketone Synthon

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Abstract: N,N'-Dimethoxy-N,N'-dimethylethanediamide on treatment with one to two equivalents of alkyl, aryl, and benzyl Grignard reagents provide α -oxo-N-methoxy-N-methylamides in good to excellent yields and on reaction with excess aryllithiums furnish moderate to good yields of symmetrical 1,2-diarylketones.

The usefulness of α -oxo amides in organic synthesis is well documented.¹ Similarly, 1,2-diketones² are also useful functional groups and recently peptidyl 1,2-diketones have been shown to be potent inhibitors of proteinases.³ Therefore development of new methodologies for the preparation of these functionalities is important. The use of N,N'-tetramethylethanediamide as an α -oxo amide synthon has been evaluated by Campaigne,⁴ and the applicability of this compound as a 1,2-dicarbonyl synthon was not tested in this study. We have examined the utility of N,N'-dimethoxy-N,N'-dimethylethanediamide as a synthon for the preparation of α -oxo-N-methoxy-N-methylamides and symmetrical 1,2-diketones (Scheme 1).

Scheme 1



After the initial report of Nahm and Weinreb⁵ on the use of N-methoxy-N-methyl amides as a carbonyl equivalent, this strategy has found wide applications in a variety of syntheses.⁶ For example, Hlasta⁷ and Reich⁸ have independently shown that N,N'-dimethoxy-N,N'-dimethylurea functions as a carbon dioxide equivalent providing unsymmetrical ketones on sequential treatment with two different nucleophiles. The underlying basis for the usefulness of N-methoxy-N-methylamides as a carbonyl equivalent is the formation of a stable chelated intermediate after nucleophilic attack, preventing further additions, and thus minimizing the amount of side products. Evans has shown that the stability of these chelated intermediates are quite high and will allow for further manipulations of remote centers under highly basic conditions.⁹ The use of N-methoxy-N-methylamides as a carbonyl synthon can be problematic in some cases where bulky nucleophiles are employed resulting in the formation of formaldehyde and the N-methylamide.¹⁰ In this letter, we describe the successful preparation of a variety of α -oxo-N-methoxy-N-methylamides and 1,2-diarylketones.

N,N'-Dimethoxy-N,N'-dimethylethanediamide¹¹ is readily prepared in very high yields (95% recrystallized) from oxalylchloride and N,O-dimethylhydroxylamine hydrochloride following the procedure of Weinreb.⁵ Treatment of a solution of this amide with one to two equivalents of a nucleophile¹² under a variety of reaction conditions followed by acidic workup provides α -oxo-N-methoxy-N-methylamides.¹³ Table 1 lists the results from these experiments.

Table 1. Synthesis of α-oxo-N-Methoxy-N-Methylamides



Entry	Reagent	# of Equivalents	Temp., °C	Solvent	Time	Yield, 2 ^a	Yield, 3ª
1	PhMgBr	1.5	0	THF	1 h	95	
2	PhMgBr	1.5	25 ^b	Ether	2 h	93	
3	PhMgBr	1.5	0	DME	2 h	90	
4	PhLic	1.05	-78	THF	3 h	70	
5	4-Cl-PhMgBr	1.5	0	THF	1 h	88	
6	4-Cl-PhLi	1.5	-78	THF	1 h	90	
7	4-H ₃ C-PhMgBr	1.5	0	THF	2 h	94	
8	BenzylMgBr	1.5	0	THF	1 h	61	12
9	CvclohexvlMgBr	2.0 ^d	0	THF	2 h	70	6
10	HexvlMgBr	1.2	0	THF	1 h	84	
11	n-BuMgBr	1.5	0	THF	0.5 h	75	
 12	n-BuLie	1.05	-78	THF	0.8 h	14	10

Key: ^aYields are for isolated and column purified or recrystallized materials. ^b The starting amide is very sparingly soluble in ether at 0 °C. Reaction at 0 °C gave 53 % of the oxo amide and 40% of starting material. ^C 8% of benzil is also formed. ^d The reaction did not go to completion with 1-1.5 equivalents of the Grignard. ^e 15% of 5,6-decanedione is also formed.

Several points in Table 1 are noteworthy. The preparation of oxo amides proceed in good to excellent yields with a variety of nucleophiles (aryl, alkyl, secondary alkyl, and benzyl) under mild reaction conditions. The nucleophile of choice in these reactions are the Grignard reagents and not the corresponding organolithiums (compare entries 1 and 4; 11 and 12), and the reactions with the Grignard reagents are cleaner providing the oxo amides in good yields with very few byproducts. The nucleophilic additions proceed equally well in different solvents (entries 1, 2, 3). In reactions with some nucleophiles, the secondary amide 3 is obtained as a minor product resulting from proton abstraction from the methoxyl group and loss of formaldehyde (entries 8, 9, and 12). Similar observations have been made by Graham in his recent studies on thiophenesulfonamides.¹⁰ Formation of the oxo amide is very sluggish in the case of allyl magnesium chloride furnishing several products.

During the preparation of the α -oxo amides using organolithium reagents, we observed the formation of 1,2-diketones as minor products. In order to exploit this observation, we carried out nucleophilic additions to diamide 1 under forcing conditions using both organo lithiums and Grignard reagents. The results from these experiments are listed in Table 2.

Table 2. Preparation of 1,2-diketones



Entry	Reagent	# of Equivalents	Temp., °C	Solvent	Time	Yield, 4 ^a	Yield, 3ª
1	PhMgBr	4	65	THF	7 h	62	21
2	PhLi	5	-78 to RT	THF	15 h	76	2
3	4-CH ₃ -PhMgBr	5	65	THF	4 h	48	48
4	4-CH ₃ -PhLi	6	-60	THF	3 h	86	4
5	4-Cl-PhMgBr ^b	5	65	THF	7 h	0	17
6	4-Cl-PhLi	4	-60	THF	5 h	66	9
7	2-OCH3-PhLi	6	-60	THF	8 h	52	4
8	4-OCH ₃ -PhLi	6	-78 to RT	THF	20 h	41	13
9	n-BuLi ^c	3	-78	THF	5 h	17	9

Key: ^a Yields are for isolated and column purified or recrystallized materials. ^b The amide 2 is formed in 58% yield. ^c The amide 2 is also formed in 12% yield.

Some trends can be discerned from Table 2. The formation of the 1,2-diketones proceed in moderate to good yields for a variety of aryllithiums. Unlike the preparation of the α -oxo amides, the nucleophile of choice for the preparation of 1,2-diketones are the organolithiums (compare entries 1 and 2; 3 and 4; 5 and 6). The differences in reactivity of Grignard and lithium reagents is quite apparent in the case of 4-chlorophenyl compound where the Grignard reagent produced no diketone (entries 5 and 6). However, the anomaly in reactivity exhibited by phenyl magnesium bromide and p-tolyl magnesium bromide as compared to p-chlorophenyl magnesium bromide remains unexplained. Reaction with excess butyl lithium did produce 5,6-deacanedione, albeit in low yields (entry 9).¹⁴ On the other hand, alkyl and benzyl Grignards under forcing conditions (5 eq., reflux in THF) gave the α -oxo amides, N-methyl amides, decomposition products, and none of the 1,2-diketones.¹⁵

In conclusion, we have shown that N,N'-dimethoxy-N,N'-dimethylethanediamide functions well as a α -oxo amide and 1,2-dicarbonyl synthon. Extension of these studies for the preparation of unsymmetrical 1,2-diketones, 1,2,3-tricarbonyl compounds, and reduction of α -oxo amides to α -hydroxy aldehydes are currently underway in our laboratory.

Acknowledgement: We thank North Dakota State University and NSF-EPSCoR for providing financial support. Partial support for this work was provided by the NSF's Instrumentation and Laboratory Improvement Program through grant #USE-9152532.

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- 11. For a low yield synthesis of this compound see: Bartos, V. A.; Bliefert, C. Chem.-Ztg. 1986, 110, 127.
- 12. In several experiments, inverse addition; i.e, addition of the amide to the Grignard reagents, did not result in variation of yields or the nature of the products formed.
- 13. All new compounds prepared showed physical, spectral (IR, NMR, MS), and analytical data consistent with their structure.
- 14. These reactions are unoptimized.
- 15. For example: reaction with benzyl magnesium bromide gave 49% of oxo amide and 42% of N-methyl amide; hexyl magnesium bromide gave 27% oxo amide and 9% N-methyl amide.

(Received in USA 19 December 1991)