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A SIMPLE SYNTHESIS OF SYMMETRICAL α-DIONES FROM ORGANOMETALLIC REAGENTS AND 1,4-DIMETHYL-PIPERAZINE-2,3-DIONE

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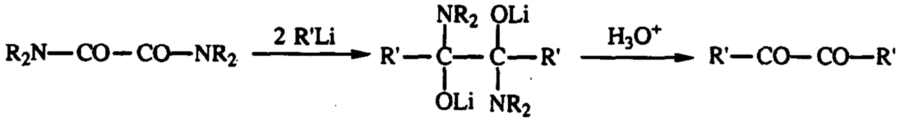
Abstract: *Short reflux of an equimolar mixture of N,N'-dimethyl ethylenediamine and diethyl oxalate in i-propanol or diethyl ether leads to 1,4-dimethyl-piperazine-2,3-dione, which is able to react with two equivalents of organolithium or Grignard compounds to form symmetrically substituted α-diones in excellent yields.*

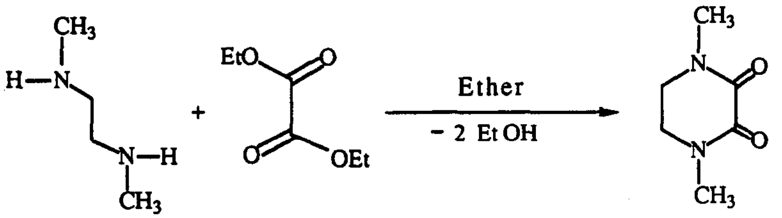
The addition of Grignard or organolithium compounds to dimethyl formamide is the first step in a frequently used aldehyde synthesis.[1] The success of this method rests with the stability of the primary addition product, which avoids multiple additions of R-Li or R-MgBr. It would therefore seem possible that this synthetic principle could be extended to the preparation of α-diones by adding organometallic compounds to tetrasubstituted oxamides (eq 1). In spite of the fact that α-diones are highly desirable intermediates in the synthesis of a wide range of materials,[2] the reaction of eq 1 does not seem to have been realized so far, although several other, more or less general, direct syntheses of α-diones are known.[3]



$$R_2N{-}CO{-}CO{-}NR_2 \xrightarrow{2\ R'Li} R'{-}\overset{NR_2}{\underset{OLi}{C}}{-}\overset{OLi}{\underset{NR_2}{C}}{-}R' \xrightarrow{H_3O^+} R'{-}CO{-}CO{-}R' \qquad (1)$$

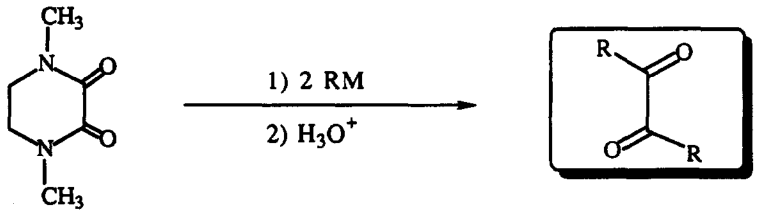
We wish to report how this idea can be realized in an effective way, but that, in spite of this, there are two reasons why the simple principle of eq 1 is not workable: (1) tetra-alkyl or alkyl-aryl oxamides are not all that easily obtainable; (2) the known ones do not produce α-diones. Dialkyl oxalates usually react with secondary amines only on one ester function to produce the ester amides.[4] The only exception is the reaction of diethyl oxalate with piperidine at reflux.[5] Early on, Tchugaeff [3a] mentioned plans to treat this diamide with Grignard reagents to prepare α-diones (according to eq 1) but evidently did not succeed and never published the results. Our re-investigation has shown that the reaction of oxalic dipiperidide with Ph-Li does not lead to benzil at all. Depending on the reaction conditions, either the benzoyl carboxamide or benzophenone are formed instead. The latter was shown to be formed from the carboxamide under the reaction conditions.[6]

Our results concern two surprising reactions which, when applied in sequence, constitute a very simple synthesis of symmetrically substituted α-diones according to eq 1. The first reaction (eq 2) is the unexpectedly simple synthesis of 1,4-dimethyl-piperazine-2,3-dione (1, "DMPD"); the second one (eq 3) concerns the addition of organolithium compounds or Grignard reagents to DMPD to produce α-diones in excellent yield



1, "DMPD"

(2)



(3)

In spite of the reluctance of diethyl oxalate to react with secondary amines to form bis-amides, we were able to obtain the cyclic, cis-fixed oxamide **1** in the seemingly much more demanding and unlikely reaction of N,N'-dimethyl ethylenediamine and diethyl oxalate in refluxing ether or i-propanol.[7] The purified product (colorless crystals, m.p. 178°C) formed in excellent yield (>90%). Polymer or oligomer formation was not observed.

The easily accessible DMPD seemed to be a good substrate for reactions with two equivalents of an organolithium or Grignard reagent, which would constitute a very general synthetic method for α-diones. As a first test, phenyl lithium was reacted with DMPD in THF at room temperature. Hydrolysis, chromatography and recrystallization of the yellow product produced pure benzil in 95% yield. Similar reactions according to eq 3 with a sampling of different organometallic compounds were equally successful under the following conditions: a slurry of DMPD in ether or THF was stirred at room temperature while a solution of two equivalents of R-Li or R-Mg-Br was gradually added; after 30-60 minutes the mixture was hydrolyzed with 10% HCl and worked up; chromatography and distillation or recrystallization led to the pure products. The results are summarized in Table 1.

TABLE 1: Typical Reactions of DMPD (**1**) with Organometallics

Organometallic Reagent (equiv.)	Solvent	Time/Temp. (min/°C)	Product	Yield[a] (%)
C_6H_5-Li (2)	THF	30/20	Ph-CO-CO-Ph	95
C_6H_5-Mg-Br (2)	THF	60/20	Ph-CO-CO-Ph	84
C_4H_9-Li (2)	Ether	30/20	Bu-CO-CO-Bu	92
n-$C_{10}H_{21}$-MgBr (2)	THF	60/20	$C_{10}H_{21}$-CO-CO-$C_{10}H_{21}$	70
CpFeCp-Li (2)	THF	90/-78-20	CpFeCp-CO-CO-CpFeCp	85
1. C_6H_5-Li (1) 2. C_4H_9-Li (1)	THF	60+30/20	Ph-CO-CO-Bu	20[b]

a. Yields are based on recrystallized or distilled pure products.

b. The symmetrical α-diones are the major products: Ph-CO-CO-Ph (40%), Bu-CO-CO-Bu (30%).

To test the possibility that unsymmetrically substituted α-diones could also be obtained in this way, two different organolithium species were added in sequence: slow addition of one equivalent of Ph-Li to a partial suspension of DMPD in THF, followed by addition of one equivalent of Bu-Li, was expected to lead to 1-phenyl-hexane-1,2-dione. However, the reaction produced only a low yield of the desired product and the main product was benzil. In order to be successful, this reaction must allow the reaction between one equivalent each of Ph-Li and DMPD to be specific and complete before Bu-Li can be added in the second step. Because DMPD is only sparingly soluble in aprotic solvents at room temperature, the initial reaction with Ph-Li is heterogeneous and two equivalents of Ph-Li can easily add to DMPD (preferred formation of benzil) even with a very slow addition of Ph-Li; upon addition of Bu-Li, the unreacted DMPD forms decane-4,5-dione; only a small amount of product is formed by the desired addition of both organometallics.

For the direct synthesis of symmetrical α-diones from organometallic reagents, DMPD thus seems to be the most useful reagent to date. To overcome the problems in the preparation of unsymmetrically substituted α-diones, we have investigated the synthesis and reactions of analogs of 1 with higher solubility in these solvents. Such reagents will allow the additions of R-Li to be conducted in a homogeneous manner and to thus allow the synthesis of symmetrical and unsymmetrical α-diones with equal success. The results will be reported separately.

The reason why DMPD so effectively produces α-diones whereas oxalic dipiperidide fails are directly linked to the near-planar structure of DMPD, which allows the required double addition of R-Li (or R-Mg-Br) to occur in the sterically more favored trans orientation. The steric problems of the oxalyl dipiperidide reactions are therefore avoided, and the reaction does not stop after the addition of one equivalent of R-Li.

References and Notes:

1. (a) Wakefield, B. J. *Organolithium Methods*, Academic Press, New York, 1988; (b) Wakefield, B. J. *The Chemistry of Organolithium Compounds*, Pergamon, Oxford, 1974; (c) Houben-Weyl, *Methoden der Organischen Chemie*, Thieme Verlag, Stuttgart, 1974, 4th ed., Vol. XIII/1; (d) Schlosser, M. *Polare Organometalle*, Springer Verlag, Berlin, 1973.
2. Krongauz, E. S. *Russian Chem. Rev.* **1977**, *46*, 1.
3. (a) Tschugaeff, L. *Chem. Ber.* **1907**, *40*, 186-187; (b) Braun, W. Ger. Patent # 913891 (21. June 1954); *Chem. Abst.* **1956**, *52*, 14691f; (c) Girard, P.; Couffignal, R.; Kagan, H.B. *Tetrahedron Lett.* **1981**, *22*, 3959; see also: Kagan, H. B. et al, *Tetrahedron Lett.* **1984**, *25*, 2869; **1989**, *30*, 7407; **1991**, *56*, 3118; (d) Olah, G. A.; Wu, A.-H. *J. Org. Chem.* **1991**, *56*, 902-904.
4. Beilstein's "Handbuch der Organischen Chemie" mentions tetramethyl oxamide [H4, 62] having been obtained from N,N-dimethyl carbamic acid chloride and sodium in ether; A. W. v. Hofmann prepared the half-amide Et_2N-CO-CO-OEt in the reaction of the diethyl oxalate and diethyl amine: *J. Chem. Soc.* **1861**, 495; *Chem. Ber.* **1870**, *3*, 776 [Beilstein E4, 606].
5. (a) Wallach, O. *Liebigs Ann. Chem.* **1882**, *214*, 278; (b) Schotten, C. *Chem. Ber.* **1882**, *15*, 421.
6. (a) To determine why the attempt by Tschugaeff[3a] to employ oxalyl dipiperidide has never been reported, we reacted this amide with excess (up to 5 equivalents) phenyl lithium. At room temperature, the half-reacted ester-amide 1-phenyl-2-piperidyl-ethane-1,2-dione was formed; traces of benzil and minor amounts of benzophenone were also observed. Extended reaction times (5 hrs) and elevated temperatures (reflux) led to the complete conversion of the half-amide to benzophenone. Evidently, the product of the first addition of phenyl lithium is too bulky to allow a second addition to complete the reaction. A similar result was obtained, when the sterically less demanding BuLi was used in this reaction, although the reaction appears to be more complicated. Very slow addition of 2 equivalents of BuLi to the diamide in ether at room

temperature mainly produced the ester-amide Bu-CO-CO-piperidine and a small amount of 5,6-dibutyl-decane-5,6-diol as an unexpected byproduct. Longer reaction times and use of excess BuLi made the latter become the major reaction product. The expected reaction product decane-5,6-dione was observed only in minor percentages, although it must be a reaction intermediate in the formation of the above diol. (b) The formation of an aroyl carboxamide has also been reported in the reaction of an aryl lithium compound with tetramethyl oxamide: Campaigne, E.; Rogers, R. B. *J. Heterocycl. Chem.* **1973**, *10*, 297.

7. (a) The synthesis of **1** was mentioned (Nazzal, A.; Lane, R. W.; Mayerle, J. J.; Mueller-Westerhoff, U. T. *United States NTIS, Final Report USARO,* **1978**, *78*, 137; see also: Mueller-Westerhoff, U. T.; Vance, B., Chapter 16.5. in *Comprehensive Coordination Chemistry,* Wilkinson, G., Ed., Pergamon Press, 1987.) in connection with the preparation of dithiolene complexes. The reaction of **1** with P_4S_{10} led to the dithione, which was used in the formation of the complexes. At that time we did not recognize the success of this reaction as being unusual, because we were unaware of the difficulties present in the reaction of oxalic esters with other secondary amines. (b) Meanwhile, the synthesis of **1** has also been carried out elsewhere (Isaksson, R.; Liljeford, T., Sandström, J. *J. Chem. Research (S)* **1981**, 43; *J. Chem. Research (M)* **1981**, 664-682.) in a more complicated and less effective way (40% yield). The same authors also effected the conversion of DMPD to the dithione using Lawesson's Reagent.

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