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## A Direct Access to $\alpha$ -Diones from Oxalyl Chloride

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Abstract: Cross-coupling reactions of oxalyl chloride with organocopper reagents, derived from Grignard reagents, cuprous bromide, and lithium bromide, provide a simple and straightforward method for the synthesis of symmetrical  $\alpha$ -diones in very good yields.

 $\alpha$ -Diones have always attracted a great deal of interest in organic synthesis as versatile intermediates with very useful functional groups undergoing a wide variety of chemical transformations.<sup>1</sup> As a consequence several synthetic approaches have been elaborated for their synthesis.<sup>2</sup> However, only a few of these methodologies employed an oxalyl derivative as the source of the  $\alpha$ -dicarbonyl moiety. Indeed, it has been found<sup>3</sup> that N,N'-dimethoxy-N,N'-dimethylethanediamide led to symmetrical  $\alpha$ -diones in moderate to good yields using an excess of organolithium or Grignard reagents, whereas symmetrical diaryl  $\alpha$ -diones<sup>4</sup> can be obtained in reasonable good yields by reacting of 1,1'-oxalylimidazole with two equivalents of an aryl Grignard reagent. Recently, Mueller-Westerhoff<sup>5</sup> has found that symmetrical and unsymmetrical  $\alpha$ -diones can be conveniently synthesized from 1,4-dialkylpiperazine-2,3-dione and RLi or RMgBr. The use of oxalyl chloride, the most prototypal and more readily available starting material for this purpose, has been reported only in one example<sup>6</sup> involving dibutylcadmium as a reagent for the synthesis of 5,6-decandione (yield 37%), but its application is limited by the type of reagent.

In the course of our extensive work<sup>7</sup> in the area of the direct acylation of organometallics we had experienced the importance of the nature of the reagents and of the catalyst for the success of the coupling. Therefore we considered challenging the search for a direct approach to  $\alpha$ -diones according to the equation 1:



The first experiments were carried out with Grignard reagents, in the presence of Ni, Pd or Fe complexes as catalysts, or organocuprates which did not allow the expected substitution to occur to any significant extent. Better conversions were obtained with organocopper reagents, generated from Grignard reagents and CuI, but  $\alpha$ -diones were isolated in poor yields. In order to optimize these results, we tested various copper salts (e.g. CuBr, CuBr, Me<sub>2</sub>S, CuCN) for preparing the organocopper reagents. Finally, we found that the process can be

performed in a convenient manner by the use of organocopper reagents derived from Grignard reagents, cuprous bromide, and lithium bromide (eq. 2):

$$\begin{array}{c} Cl \\ 0 \\ 0 \\ 1 \end{array} \qquad \begin{array}{c} RMgBr \cdot CuBr \cdot 2LiBr \\ THF \\ 0 \\ 1 \end{array} \qquad \begin{array}{c} 0 \\ R \\ 0 \\ 2 \text{ a-k} \end{array}$$
(2)

A typical experimental procedure is as follows: a THF solution of anhydrous LiBr (30 mL, 16.52 mmol) was added at room temperature, under nitrogen, to a stirred suspension of CuBr (1.19 g, 8.26 mmol) in THF (30 mL). The resulting mixture was stirred at the same temperature until it became homogeneous, then cooled at 0°C. A 0.86 M freshly prepared solution of 2-thienylmagnesium bromide in THF<sup>8</sup> (9.6 mL, 8.26 mmol) and soon afterwards oxalyl chloride in THF (15 mL, 3.44 mmol) were quickly added to the stirred solution of salts. The mixture was stirred at 0°C for 15 min, quenched with saturated aqueous NH<sub>4</sub>Cl and extracted with ethyl acetate. The organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The residue was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate 9.5/0.5) leading to di-2-thienylethanedione (thenil) **2a** (749 mg, 98% yield) as a yellow solid, mp 81-82°C (lit. mp 81-82°C<sup>9</sup>, 83-84 °C<sup>10</sup>); <sup>1</sup>H NMR data (200 MHz, CDCl<sub>3</sub>):  $\delta$  7.21 (dd, J = 4.8, 3.9 Hz, 2H), 7.85 (dd, J = 4.8, 1.0 Hz, 2H), 8.07 (dd, J = 3.9, 1.0 Hz, 2H) ppm; MS (70 eV); m/z (%) 222 (M<sup>+</sup>, 10), 111 (100), 83 (10), 39 (27).

Other results are listed in the Table. The use of LiBr is critical because the absence of LiBr (entry 1) led to very low conversion giving a mixture of  $\alpha$ -dione, ketone and a large amount of homocoupling product. We found that the optimum conditions to produce  $\alpha$ -diones in high yields is the use of an organocopper compound prepared from equivalent amounts of Grignard reagent and CuBr and two equivalents of LiBr. The reaction is very simple and appears to be of wide scope. Aliphatic, aromatic, alicyclic and heterocyclic organocopper reagents can be efficiently used, including relatively sterically hindered species (entry 7). In all the cases examined the cross-coupling reactions were very clean, leading to essentially pures symmetrical  $\alpha$ -diones,<sup>11</sup> which were contaminated only by small amounts of homocoupling products. The products **2a-k** were easily purified by flash chromatography on a silica gel column and their structures were confirmed on the basis of spectral data.

In conclusion, a simple and convenient method to obtain  $\alpha$ -diones directly from oxalyl chloride is now available. A Grignard reagent is transformed into an organocopper species which, in the presence of LiBr, allows the expected cross-coupling reaction to occur to a satisfactory extent. This new process appears to be competitive with/or superior to other methods previously reported due to attractive synthetic advantages such as simplicity, high yields, and availability of starting materials.

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Entry	R	Products 2a-ka	Temp.	Yield (%) <sup>b</sup>
1	2-Thienyl <sup>c</sup>	S 2a	0°C	12 d
2	2-Thienyl	Za za	0°C	98
3	Phenyl	2b	0°C	75
4	<i>o</i> -Tolyl	2c	0°C	85
5	<i>m</i> -Tolyl	2d	0°C	82
6	<i>p</i> -Tolyl	2e	0°C	80
7	2- <i>m</i> -Xylyl	2f	0°C	97
8	p-Methoxyphenyl	MeO 2g	0°C	90
9	Octyl		-78°C e	75
10	Decyl	2i	-78°C e	80
11	3-Pentyl	J 2j	-78°C ¢	80
12	Cyclohexyl	Que la construction de la const	-78°C e	75

 Table. Typical reactions of oxalyl chloride with organocopper reagents derived from RMgBr, CuBr, and LiBr (1:1:2).

a) All compounds exhibited spectral data consistent with the assigned structure. b) Yields refer to products purified by flash chromatography. c) Reaction carried out in absence of LiBr. d) Determined by GLC. The main products are 2,2'-dithienyl and di-2-thienyl ketone. e) At 0°C the reaction leads to a relevant amount of the homocoupling product and to a low yield of the  $\alpha$ -dione.

## **References and Notes**

- Krongauz, E.S. Russ. Chem. Rev. 1977, 46, 59-75; Venkatachalam, M.; Deshpande, M.N.; Jawdosiuk, M.; Kubiak, G.; Wehrli, S.; Cook, J.M. Tetrahedron 1986, 42, 1597-1605 and references cited therein; De Kimpe, N.; Stanoeva, E.; Boeykens, M. Synthesis, 1994, 427-431 and references cited therein.
- For some recent methodologies used to synthesize α-diones, see: Girard, P.; Couffignal, R.; Kagan, H.B. Tetrahedron Lett. 1981, 22, 3959-3960; Nudelman, N.S.; Outumuro, P. J. Org. Chem. 1982, 47, 4347-4348; Leyendecker, J.; Niewöhner, U.; Steglich, W. Tetrahedron Lett. 1983, 24, 2375-2378; Petrakis, K.S.; Batu, G.; Fried, J. Tetrahedron Lett. 1983, 24, 3063-3064; Souppe, J.; Namy, J-L.; Kagan, H.B. Tetrahedron Lett. 1984, 25, 2869-2872; Carre, M.C.; Caubere, P. Tetrahedron Lett. 1985, 26, 3103-3106; Verlhac, J.-B.; Chanson, E.; Jousseaume, B.; Quintard, J.-P. Tetrahedron Lett. 1985, 26, 6075-6078; Bumagin, N.A.; Gulevich, Yu.V.; Beletskaya, I.P. J. Organomet. Chem. 1985, 282, 421-425; Conrow, R.; Portoghese, P.S. J. Org. Chem. 1986, 51, 938-940; Ballistreri, F.P.; Failla, S.; Tomaselli, G.A.; Curci, R. Tetrahedron Lett. 1986, 27, 5139-5142; Amon, C.M.; Banwell, M.G.; Gravatt, G.L. J.Org. Chem. 1987, 52, 4851-4855; Murakami, M.; Masuda, H.; Kawano, T.; Nakamura, H.; Ito, Y. J. Org. Chem. 1987, 56, 1-2; Olah, G.A.; Wu, A. J. Org. Chem. 1991, 56, 902-904; Seyferth, D. Weinstein, R.M.; Hui, R.C.; Wang, W.-L.; Archer, C.M. J. Org. Chem. 1991, 56, 5768-5773; Punniyamurthy, T.; Kalra, S.J.S.; Iqbal, J. Tetrahedron Lett. 1994, 35, 2959-2960; Iwahama, T.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. Tetrahedron Lett. 1995, 36, 1523-.1526.
- 3. Sibi, M.P.; Sharma, R.; Paulson, K.L. Tetrahedron Lett. 1992, 33, 1941-1944.
- 4. Mitchell, R.H.; Iyer, V.S. Tetrahedron Lett. 1993, 34, 3683-3686.
- Mueller-Westerhoff, U.T.; Zhou, M. Tetrahedron Lett. 1993, 34, 571-574; Mueller-Westerhoff, U.T.; Zhou, M. J. Org. Chem. 1994, 59, 4988-4992; Mueller-Westerhoff, U.T.; Zhou, M. Synlett 1994, 975-984.
- 6. Kollonitsch, J. J. Chem. Soc. (A) 1966, 456-458.
- Fiandanese, V.; Marchese, G.; Ronzini, L. Tetrahedron Lett. 1983, 24, 3677-3680; Fiandanese, V.; Marchese, G.; Martina, V.; Ronzini, L. Tetrahedron Lett. 1984, 25, 4805-4808; Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Ronzini, L. Tetrahedron Lett. 1985, 26, 3595-3598; Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Ronzini, L. Tetrahedron Lett. 1987, 28, 2053-2056; Fiandanese, V.; Marchese, G.; Naso, F. Tetrahedron Lett. 1988, 29, 3587-3590; Babudri, F.; D'Ettole, A.; Fiandanese, V.; Marchese, G.; Naso, F. J. Organomet. Chem. 1991, 405, 53-58; Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. Synlett 1994, 719-720.
- 8. The use of ether solutions of the Grignard reagents led to lower yields of  $\alpha$ -diones.
- 9. Deschamps, I.; King, W.J.; Nord, F.F. J. Org. Chem. 1949, 14, 184-187.
- 10. Cardon, S.Z.; Lankelma, H.P. J. Am. Chem. Soc. 1948, 70, 4248-4249.
- 11. We have also tested the possibility of obtaining unsymmetrical substituted  $\alpha$ -diones. Two different organocopper reagents were added sequentially to oxalyl chloride. However, the reaction produced generally a mixture of symmetrical and unsymmetrical substituted  $\alpha$ -diones in comparable amounts (GC analysis). When the two different organometallic reagents were both of the aliphatic type, only symmetrical  $\alpha$ -diones were obtained.