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Synthesis of 1,4-diketones: reaction of α-bromo ketones with tetrakis(dimethylamino)ethylene (TDAE)

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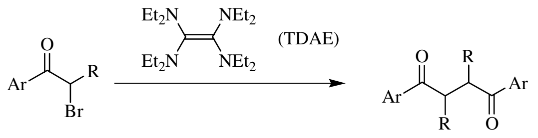
Abstract—1,4-Diketones were prepared by the reaction of α-bromo ketones with tetrakis(dimethylamino)ethylene (TDAE) in moderate to good yields. Similarly, α-bromo esters were reductively coupled using TDAE to give the 1,4-diesters in moderate yields.

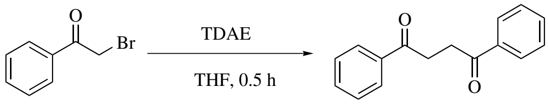
1,4-Diketones are widely used as a synthetic intermediate in the preparation of five-membered cyclic- and heterocyclic compounds, such as cyclopentanones, furans, and pyrroles;[1] thus the development of the synthetic methods of the 1,4-diketones could have a significant impact on organic chemistry. A number of methods for the synthesis of 1,4-diketones have already been reported, and among them, the use of α-halo ketones as the starting material seems to be one of the most versatile processes in organic synthesis.[2,3] A number of homo-coupling reactions of α-halo ketones giving 1,4-diketones are shown; however there are some disadvantages, that is, (i) limitation of substrates, (ii) the use of an excess amount of metal, (iii) low or moderate yields of products, and (iv) multi-step procedures.

We have recently found that tetrakis(dimethylamino)ethylene (TDAE) was an efficient agent for the reductive debromination of 1,2-bis(bromomethyl)arenes.[4,5] Based on our continuous study on the utilization of TDAE in organic synthesis, we have now developed an efficient synthetic method of 1,4-diketones by the reaction of α-halo ketones with tetrakis(dimethylamino)ethylene (TDAE) (Scheme 1).



Scheme 1.

Table 1. Reaction of 2-bromoacetophenone with TADE[a]



1 2

Entry	Temperature (°C)	Additive (mmol)	Yield[b] (%)
1	25	—	2
2	40	—	29
3	67	—	60
4	67	I_2 (0.04)	92

[a] Reaction conditions: **1** (1.0 mmol), TDAE (0.6 mmol), and THF (5 mL) for 0.5 h.

[b] GC yield based on α-bromoacetophenone.

When 2-bromoacetophenone (**1**) (1.0 mmol) was allowed to react with TDAE (0.6 mmol) in THF (5 ml) solvent at 67 °C for 0.5 h, the reductive coupling product, 1,4-diphenyl-1,4-butanedione (**2**), was obtained in 60% yield (based on **1**) (entry 3 in Table 1). The yield of **2** significantly decreased when the reaction was carried out at lower temperature (25 and 40 °C) (entries 1 and 2). The yield was improved by the addition of a catalytic amount of iodine, giving **2** in 92% yield (entry 4).

In order to determine the applicability of the preparation of 1,4-diketones, various α-halo ketones were allowed to react with TDAE, and the results are shown in Table 2. Contrary to that of α-bromoacetophenone, for the α-chloroacetophenone, the reaction did not proceed and the starting material (89%) was recovered

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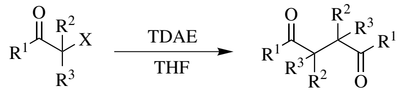
Table 2. Synthesis of 1,4-diketones[a]



Entry	R^1	R^2	R^3	X	Yield[b] (%)
1	C_6H_5	H	H	Br	94
2	C_6H_5	H	H	Cl	1
3[c]	C_6H_5	CH_3	H	Br	71
4	$4\text{-}CH_3C_6H_4$	H	H	Br	76
5	$4\text{-}CH_3OC_6H_4$	H	H	Br	69
6	$4\text{-}BrC_6H_4$	H	H	Br	2
7[d]	C_6H_5	CH_3	CH_3	Br	0
8	$2\text{-}C_{10}H_7$	H	H	Br	75

[a] Reaction conditions: α-halo ketone (1.0 mmol), TDAE (0.6 mmol), I_2 (0.04 mmol), $MgSO_4$ (2.0 mmol), and THF (5 ml) at 67 °C for 0.5 h.

[b] GC yield based on α-halo ketone.

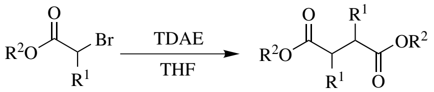
[c] The ratio of *dl*/*meso* isomer was 3.0/1.0.

[d] Isobutylophenone (11%) and 2-methyl-1-phenyl-propenone (3%) were formed.

(entry 2). For the reaction of 2-bromo-4′-methyl- and 2-bromo-4′-methoxyacetophenone, the corresponding 1,4-diketones were obtained in 76% and 69% yields, respectively (entries 4 and 5). For 2-bromo-4′-bromoacetophenone, the yield of the 1,4-diketone was low due to the preparation of complicated by-products (entry 6). Similarly, α-bromopropiophenone was reductive coupled to give 1,4-diphenyl-2,3-diethyl-1,4-butanedione in 71% yield with a mixture of *dl* and *meso* isomers (*dl*:*meso* = 3:1) (entry 3). For the reaction of the steric hindered α-bromo ketone such as α-bromo-isobutylophenone, various side reactions occurred (isobutylophenone (11%) and 2-methyl-1-phenylpropenone (3%)) and 1,4-diketone was not formed (entry 7). 1,4-Bis(2-naphthyl)-1,4-butanedione was obtained in 75% yield by the reaction of 2-bromoacetonaphthone with TDAE (entry 8). In contrast to that of the α-bromo aryl alkyl ketone, in the case of the α-bromo dialkyl ketone such as 2-bromo-3-pentanone, the yield of 1,4-diketone was low (12%) due to the preparation of complicated by-products.

The treatment of the α-bromo esters with TDAE was then examined in order to determine the scope and limitation of the reductive coupling using TDAE (Table 3). When the α-bromo acetic acid ethyl and phenyl esters were allowed to react with TDAE at 67 °C for 3 h, the succinic acid diethyl ester and diphenyl ester were obtained in 43% and 32% yields, respectively. The yields of the diesters were improved by the addition of $MgSO_4$ (entries, 1 and 3). Similarly, the 2-bromopropionic acid ethyl ester was reductively coupled to give the corresponding 1,4-diesters with a mixture of *dl* and *meso* isomers (*dl*:*meso* = 1.8:1) in 45% yield (entry 2).

Table 3. Synthesis of 1,4-diesters[a]



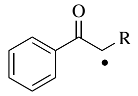
Entry	R^1	R^2	Yield[b] (%)
1	H	C_2H_5	52
2	CH_3	C_2H_5	45[c]
3	H	C_6H_5	38

[a] Reaction conditions: α-bromo ester (1.0 mmol), TDAE (0.6 mmol), I_2 (0.04 mmol), $MgSO_4$ (2.0 mmol), and THF (5 ml) at 67 °C for 3 h.

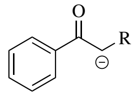
[b] GC yield based on α-bromo ester.

[c] The ratio of *dl*/*meso* isomer was 1.8/1.0.

We cannot show the detailed reaction pathway, however, two possible reaction pathways are suggested for the reaction. From the result of the reaction of the α-bromo-isobutylophenone, it was suggested that the formation of the α-carbonyl alkyl radical (**3**) by the reductive debromination of the α-bromo ketone with TDAE was the first step in the reaction.[10] Then after, **3** was coupled to give the 1,4-diketones. Another electron reduction of **3** with TDAE or the [TDAE] cation radical species produced the enolate anion (**4**), followed by nucleophilic substitution of the α-halo ketone to produce the 1,4-diketones.



3



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In summary, we found that the reductive coupling of α-bromo ketones or esters was successfully achieved using tetrakis(dimethylamino)ethylene (TDAE) as the reducing agent that gave the corresponding 1,4-dicarbonyl compounds. Furthermore, the application of this reaction and elucidation of the reaction pathway are now in progress.

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References and notes

1. (a) Ellison, R. A. *Synthesis* **1973**, 397; (b) Bosshard, P.; Eugster, C. H. *Adv. Heterocycl. Chem.* **1966**, *7*, 384; (c) Baltazzi, E.; Krimen, L. I. *Chem. Rev.* **1963**, *63*, 511.
2. (a) Kondo, J.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 825; (b) Yasuda, M.; Tsuji, S.; Shigeyoshi, Y.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 7440; (c) Miura, K.; Fujisawa, N.; Saito, H.; Wang, D.; Hosomi, A. *Org. Lett.* **2001**, *3*, 2595; (d) Never, N. M.; Kel'in, A. V.; Kulinkovich, O. G. *Synthesis* **2000**, 1259; (e) Ranu, B. C.; Dutta, P.; Sarker, A. *Tetrahedron Lett.* **1998**, *39*, 9557; (f) Koga, Y.; Kusama, H.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 475; (g) Yasuda, M.; Tsuji, S.; Shibata, I.; Baba, A. *J. Org. Chem.* **1997**, *62*, 8282; (h) Kel'in, A. V.; Kulinkovich, O. G. *Synthesis* **1996**, 330; (i) Yasuda, M.; Oh-hata, T.; Shibata, I.; Baba, A.; Matsuda, H.; Sonoda, N. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1180; (j) Yasuda, M.; Katoh, Y.; Baba, A.; Matsuda, H.; Sonoda, N. *J. Org. Chem.* **1994**, *59*, 4386; (k) Hill, D. H.; Perves, M. A.; Sen, A. *J. Am. Chem. Soc.* **1994**, *116*,

2889; (l) Yasuda, M.; Oh-hata, T.; Shibata, I.; Baba, A.; Matsuda, H. *J. Chem. Soc., Perkin. Trans. 1* **1993**, 859; (m) Baba, A.; Yasuda, M.; Yano, K.; Shibata, I.; Matsuda, H. *J. Chem. Soc., Perkin. Trans. 1* **1990**, 3205; (n) Jarbis, W. F.; Hoey, A. L.; Dittmer, D. C. *J. Org. Chem.* **1988**, *53*, 5750; (o) Fry, A. J.; Susla, M.; Weltz, M. *J. Org. Chem.* **1987**, *52*, 2496; (p) Iyoda, M.; Sakaitani, M.; Kojima, A.; Oda, M. *Tetrahedron Lett.* **1985**, *26*, 3719; (q) Fiorenza, M.; Mordini, A.; Papaleo, S.; Pastorelli, S.; Ricci, A. *Tetrahedron Lett.* **1985**, *26*, 788; (r) Barba, F.; Varesco, M. D.; Guirado, A. *Synthesis* **1984**, 593; (s) Chassin, C.; Schmidt, H.; Hoffmann, M. R. *J. Am. Chem. Soc.* **1974**, *96*, 606; (t) Ellison, R. A. *Synthesis* **1973**, 397.

3. (a) Enders, D.; Muller; Klein, D. *Synlett* **1998**, 43; (b) Vedejs, E.; Perry, D. A.; Wilde, R. *J. Am. Chem. Soc.* **1986**, *108*, 2985; (c) Kimpe, N. D.; Yao, Z.; Schamp, N. *Tetrahedron Lett.* **1986**, *27*, 1707.
4. Nishiyama, Y.; Kawabata, H.; Kobayashi, A.; Nishino, T.; Sonoda, N. *Tetrahedron Lett.* **2005**, *46*, 867.
5. There are some reports on the use of TDAE in organic synthesis: (i) reductive dehalogenation of α,α-difluoro- and α,α,α-trifluoro substituted alkyl bromide and iodide,[6] (ii) defluorination of fluorinated compounds,[7] (iii) reductive cleavage of chalcogen–chalcogen bond,[8] and (iv) reduction of high valent transition metal species.[9]
6. Bürger, H.; Moritz, P. *Organometallics* **1993**, *12*, 4930.
7. (a) Peng, W.; Zhu, S. *Tetrahedron* **2003**, *59*, 4395; (b) Takechi, N.; Aït-Mohand, S.; Médebielle, M.; Dolbier, W. R., Jr. *Tetrahedron Lett.* **2002**, *42*, 4317; (c) Médebielle, M.; Kato, K.; Dolbier, W. R., Jr. *Synlett* **2002**, 1541; (d) Takechi, N.; Aït-Mohand, S.; Médebielle, M.; Dolbier, W. R., Jr. *Org. Lett.* **2002**, *4*, 4671; (e) Aït-Mohand, S.; Takechi, N.; Médebielle, M.; Dolbier, W. R., Jr. *Org. Lett.* **2001**, *3*, 4271; (f) Billard, T.; Langlois, B. R.; Médebielle, M. *Tetrahedron Lett.* **2001**, *42*, 3463; (g) Petrov, V. A. *Tetrahedron Lett.* **2001**, *42*, 3267; (h) Burkholder, C.; Dolbier, W. R., Jr.; Médebielle, M.; Aït-Mohand, S. *Tetrahedron Lett.* **2001**, *42*, 3077; (i) Médebielle, M.; Keirouz, R.; Okada, E.; Ashida, T. *Synlett* **2001**, 821; (j) Yagupolskii, L. M.; Fedyuk, D. V. *Tetrahedron Lett.* **2000**, *41*, 2265; (k) Burkhorder, C.; Dolbier, W. R., Jr.; Médebielle, M. *J. Org. Chem.* **1998**, *63*, 5385; (l) Burkhorder, C.; Dolbier, W. R., Jr.; Médebielle, M. *Tetrahedron Lett.* **1997**, *38*, 821; (m) Chambers, R. D.; Gray, W. K.; Korn, S. R. *Tetrahedron* **1995**, *48*, 13167; (n) Briscoe, M. W.; Chambers, R. D.; Mullins, S. J.; Nakamura, T.; Vaughan, J. F. S.; Drakesmith, F. G. *J. Chem. Soc., Perkin. Trans. 1* **1994**, *8*, 3115.
8. (a) Pooput, C.; Médebielle, M.; Dolbier, W. R., Jr. *Org. Lett.* **2004**, *6*, 301; (b) Kolomeitsev, A.; Médebielle, M.; Kirsch, P.; Lork, E.; Röschenthaler, G.-V. *J. Chem. Soc., Perkin. Trans. 1* **2000**, *14*, 2183.
9. (a) Kuroboshi, M.; Waki, Y.; Tanaka, H. *Synlett* **2002**, 637; (b) Kuroboshi, M.; Tanaka, M.; Goto, K.; Tanaka, H. *Tetrahedron Lett.* **2000**, *41*, 81; (c) Kuroboshi, M.; Goto, K.; Mochizuki, M.; Tanaka, H. *Synlett* **1999**, 1930.
10. Although the reaction of α-bromoacetophenone with TDAE was carried out in the presence of a radical inhibitor, the yield of the diketone did not decrease.