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# Facile reduction of malonate derivatives using $NaBH_4/Br_2$: an efficient route to 1,3-diols

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**Abstract**

Borane–dimethoxyethane generated from sodium borohydride–bromine mixtures efficiently reduces a wide range of malonate derivatives to the corresponding 1,3-diols. This new reagent system represents a milder alternative to current methods available, providing the requisite 1,3-diols in higher yields over shorter reaction times.


The reduction of malonate derivatives is a convenient method for the preparation of symmetrical 1,3-diols.[1a–f] This reaction has received a significant amount of attention over recent years and has been employed in numerous synthetic efforts.[1a,b] Generally, powerful hydride reducing agents such as lithium aluminum hydride[1c] and DIBAL[1d] are employed to achieve this transformation. Unfortunately, deactivation of these basic reagents via enolization of the malonate starting materials often results in mixtures of the desired 1,3-diol products and other higher oxidation state reduction products.[1f] In an attempt to minimize the formation of undesired side products, milder reagents such as borane complexes[2a–c] have been utilized; however, extended reaction times and large reagent excesses are often required to obtain appreciable conversions.[2b,c] In some cases this has been attributed to α-deprotonation of the malonate by the borane complex.[1c,3]

Recently, we required a highly efficient reduction of malonate **1** to the corresponding diol **2**, a key intermediate in the synthesis of a potential drug candidate. Our preliminary investigations into this transformation are detailed in Table 1.

Attempts to reduce malonate **1** to diol **2** via the mixed anhydride[4] or with the strong reducing agent, superhydride[5] (Table 1, entries 1 and 2) provided none of the desired product. Although Red-Al did reduce the β-carboxyester functionality, concomitant removal of the aromatic bromide was also observed affording exclusively diol **3** (entry 3).[6] To minimize these problems, the commercially available reducing agents $BH_3$·THF[2a] and $BH_3$·DMS[2b] were investigated. Several unidentified by-products in addition to the two cyclopropyl by-products **4** and **5** (entries 4 and 5) were obtained under these conditions. These could be minimized to ca. 10% by preparing the borane solution in situ from sodium borohydride and boron trifluoride[7] complexes (entries 6 and 7); however, these conditions proved to be somewhat capricious affording the desired product in irreproducible quantities. Other methods for producing borane solutions such as sodium borohydride–iodine in THF[8] (entry 8) resulted in the formation of significant quantities of 4-iodo-butanol,[8] cyclopropane by-products **4** and **5**, and several other unidentified products in variable amounts. The formation of the 4-iodo-butanol impurity could be eliminated by employing DME as a solvent; however, significantly longer reaction times were required and increased quantities of the cyclopropane compounds **4** and **5** were observed. Interestingly, when bromine was substituted for iodine the cyclopropane by-products were only formed in

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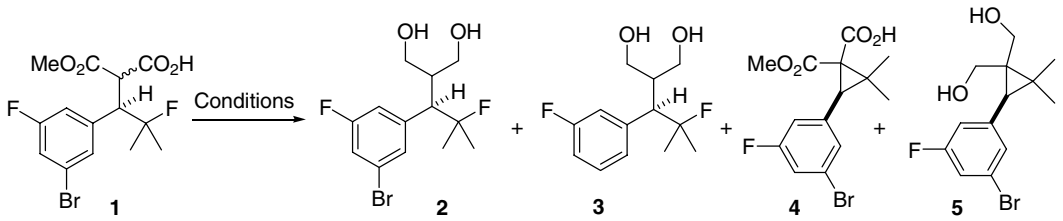
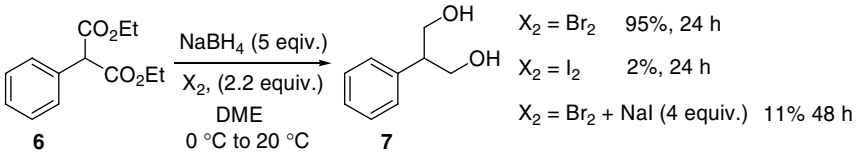
Table 1
Screen of standard reducing agents




| Entry | Conditions | Assay yield **2**[a] (%) |
|---|---|---|
| 1 | $NaBH_4$/$^tBuCO_2Cl$ | — |
| 2 | Superhydride | — |
| 3 | Red-Al | 0 |
| 4 | $BH_3$·THF | <10 |
| 5 | $BH_3$·DMS | <10 |
| 6 | $NaBH_4/BF_3{\cdot}OEt_2$ | 50–90 |
| 7 | $NaBH_4/BF_3$·THF | ~90 |
| 8 | $NaBH_4/I_2$ | 90 in THF 65 in DME |
| 9 | $NaBH_4/Br_2$ | 94–98 |

[a] Assay yield was determined by HPLC calibrated with analytically pure product.




Scheme 1.

small quantities (~5%) increasing the yield of the desired product to ~94%. Furthermore, the relative rate of the reaction was higher, resulting in reaction times of around 3–4 h versus >24 h as in the sodium borohydride–iodine reaction.

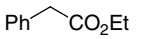
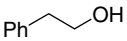
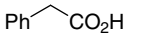
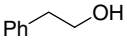
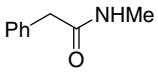
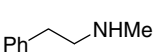
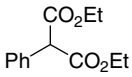
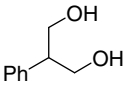
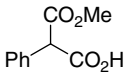
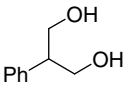
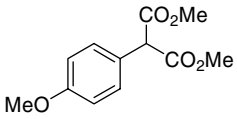
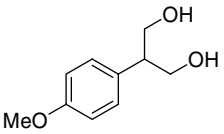
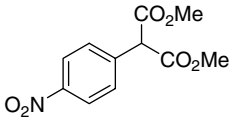
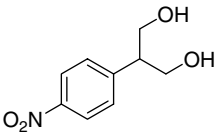
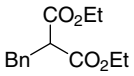
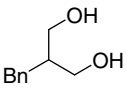
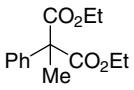
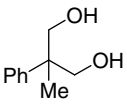
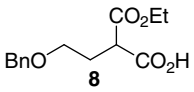
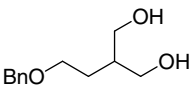
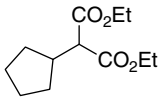
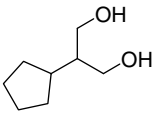
With this interesting result in hand, we decided to probe the substrate scope of this reduction. We initially investigated the curious discontinuity in rate between the reactions with iodine and bromine. As shown in Scheme 1, reduction of model diester **6** to diol **7** was carried out using the sodium borohydride–bromine and the sodium borohydride–iodine protocols described previously. As observed for the more complex malonate derivative **1**, the reduction rate of diester **6** with $NaBH_4/Br_2$ was greater than that of the $NaBH_4/I_2$ method affording 91% and 2% assay yields of diol **7**, respectively (Scheme 1). Since the sodium iodide by-product was completely solubilized in DME, we suspected that this may inhibit the reaction. Moreover, when excess sodium iodide was added to the reaction significant retardation of the rate was observed yielding only 11% of product after 48 h at room temperature further supporting our hypothesis. Indeed, theoretical studies by Frenking et al. indicated that complexation of π-donor groups such as iodide increases the hydride affinity of boron.[9] In principle, this could lead to a reducing agent with much less reduction potential than the corresponding borane–DME complex.

With a robust, practical reduction protocol established, we began to evaluate other carboxylate derivatives bearing functionality that has proven problematic for other methods. As shown in Table 2, the reaction cleanly reduced phenylacetic acid, the corresponding ethyl ester and the *N*-methylamide to their alcohol and amine products in good yield (entries 1–3). More importantly, several challenging malonate derivatives were smoothly converted to their corresponding 1,3-diols.

Hindered malonates[1b] (entry 9), electron rich aryl malonates[1b,2d] (entry 6) and nitro-aryl malonates[1b,c] (entry 7) were readily reduced to their 1,3-diol derivatives in significantly greater yield than previously obtained under existing protocols.[1b,c,2d] As expected from our lead result, reduction of other malonic acid derivatives using this protocol was readily achieved (entries 5 and 10). In particular, the reduction of malonate derivative **8** (entry 10) described by Jarvest et al. had proved to be particularly problematic only affording the desired diol in 31% yield.[10a] Pleasingly, our improved procedure provided the diol product in 87% yield.

In summary, we have developed a robust reduction of esters, acids, amides and malonate derivatives using $NaBH_4/Br_2$.[11] In particular, challenging aryl malonates proved to be excellent substrates for reduction providing the corresponding 1,3-diols in high yield. Studies are currently underway to extend the scope of this methodology

Table 2

| Entry | Substrate[a] | Product[b] | Temperature (°C)/time (h) | Isolated yield (%) |
|---|---|---|---|---|
| 1 |  |  | −10 to 20/1.5 | 92[c] |
| 2 |  |  | −10 to 20/1.5 | 93[c] |
| 3 |  |  | −10 to 20/48 | 82[d] |
| 4 |  |  | 0 to 20/24 | 91[d] |
| 5 |  |  | −10 to 20/0.5 | 92[d] |
| 6 |  |  | 0 to 20/24 | 91[d] |
| 7 |  |  | 0 to 20/4 | 92[d] |
| 8 |  |  | 0 to 20/15 | 98[d] |
| 9 |  |  | 0 to 20/15 | 91[d] |
| 10 |  |  | −10 to 20/15 | 87[d] |
| 11 |  |  | 0 to 20/15 | 88[d,e] |

[a] All substrates were obtained commercially unless otherwise indicated.
[b] All known products were characterized via direct comparison of $^1$H NMR data to the literature references detailed within the text, or commercially available samples from Aldrich Chemical Co.
[c] 2.2 equiv $NaBH_4$/1 equiv $Br_2$ required.
[d] 5 equiv $NaBH_4$/2.2 equiv $Br_2$ required.
[e] Characterized via comparison of melting point data[11] and $^1$H NMR.

into other borane mediated processes, the results of which will be reported in due course.

## References and notes


1. (a) Lee, J.; Lee, J.-H.; Kim, S. Y.; Perry, N. A.; Lewin, N. E.; Ayres, J. A.; Blumberg, P. M. *Bioorg. Med. Chem. Lett.* **2006**, *14*, 2022; (b) Katz, C. E.; Aubé, J. *J. Am. Chem. Soc.* **2003**, *125*, 13948; (c) Fellows, I. M.; Kaelin, D. E.; Martin, S. F. *J. Am. Chem. Soc.* **2000**, *122*, 10781; (d) Tercel, M.; Denny, W. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, *3*, 509; (e) Zhang, W.; Oya, S.; Kung, M.-P.; Hou, C.; Maier, D. L.; Kung, H. F. *J. Med. Chem.* **2005**, *48*, 5980; (f) Marshall, J. A.; Anderson, N. H.; Hochstetler, A. R. *J. Org. Chem.* **1967**, *32*, 113.
2. (a) Yoon, N. M.; Pak, C. S.; Brown, H. C.; Krishnamurthy, S.; Stocky, T. P. *J. Org. Chem.* **1973**, *38*, 2786; (b) Brown, H. C.; Choi, Y. M. *Synthesis* **1981**, 439; (c) Lewis, E. A.; Allan, C. C.; Boyle, R. W.; Archibald, S. J. *Tetrahedron* **2004**, *45*, 3059; (d) Choi, Y. M.; Kucharczyk, N.; Sofia, R. D. *Tetrahedron* **1986**, *42*, 6399.

3. Choi, Y. M.; Emblidge, R. W. *J. Org. Chem.* **1989**, *54*, 1198.
4. De Saint Laumer, J.-Y.; Frérot, E.; Herrmann, A. *Helv. Chim. Acta* **2003**, *86*, 2871.
5. Lane, C. F. *Aldrichim. Acta* **1974**, *7*, 32.
6. For examples of aromatic dehalogenation with aluminum hydride reagents see: Karabatsos, G. J.; Shone, R. L.; Scheppele, S. E. *Tetrahedron Lett.* **1964**, *5*, 2113.
7. (a) Brown, H. C. In *Organic Synthesis Via Boranes*; Aldrich Chemical Co.: Milwaukee, 1997; Vol. 1; (b) Kanth, J. V. B.; Brown, H. C. *Inorg. Chem.* **2000**, *39*, 1795.
8. Prasad, A. S. B.; Kanth, J. V. B.; Periasamy, M. *Tetrahedron* **1992**, *48*, 4623.
9. Frenking, G.; Fau, S.; Marchand, C. M.; Grützmecher, H. *J. Am. Chem. Soc.* **1997**, *119*, 6648.
10. (a) Jarvest, R. L.; Barnes, R. D.; Earnshaw, D. L.; O'Toole, K. J.; Sime, J. T.; Vere Hodge, R. A. *J. Chem. Soc., Chem. Cummun.* **1990**, 555; (b) Rastetter, W.; Phillion, D. P. *J. Org. Chem.* **1981**, *46*, 3204.
11. General experimental procedure, Table 2 entry 5: To a cold (−20 °C), stirred slurry of $NaBH_4$ (946 mg, 25 mmol) in DME (10 mL) was added bromine (0.565 mL, 11 mmol) dropwise over 1 h, maintaining the exotherm between −20 and −10 °C. The slurry was stirred for 1 h until the orange color disappeared to give a white slurry of sodium bromide. At this point, the slurry was warmed to −5 °C and treated with β-carboxyester **8** (971 mg, 5 mmol). The reaction was stirred for 30 min until no starting material remained by HPLC. The reaction mixture was then added into a solution pre-cooled (5 °C) 1 N HCl (15 mL) and isopropyl acetate (15 mL). The mixture was stirred for 5 min before separating the organic and washing sequentially with 2 N $K_2CO_3$ (3 × 15 mL) and water (15 mL). The organic solution was dried ($Na_2SO_4$) and concentrated to give the crude product. The crude product was recrystallized from 3:1 heptane/MTBE to afford diol **7** as a white solid. Mp: 52–53 °C, lit. 51–53 °C;[3] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.37–7.24 (5H, m, 5 × Ar*H*), 4.00 (4H, m, 2 × C$H_2$), 3.12 (1H, tt, $J = 7.5$, 5.6 Hz, C*H*), 2.02 (2H, br s, 2 × O*H*).