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Practical preparation of benzyloxyacetic acids

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Abstract

An efficient and practical method for the preparation of benzyloxyacetic acids is described. The procedure involves the reaction of readily available chloroacetic acid with benzyl alcohol in the presence of powdered KOH providing a safer alternative to the known literature procedures, which completely eliminates the use of pyrophoric bases such as sodium hydride and sodium metal.
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α-Hydroxy acids constitute the core framework of a large and diverse class of natural and unnatural products possessing a significant range of biological activities.[1] Secondary and tertiary chiral α-hydroxy acids are important synthetic intermediates and numerous methods for their construction have been developed.[2,3] Often these chiral building blocks are derived from the achiral, primary α-hydroxy acids. While glycolic acid is the simplest member of this family, protected hydroxy acids have typically been utilized in synthetic transformations due to their increased solubility in organic solvents. Substituted benzyloxyacetic acids of general type **1** have garnered a considerable amount of attention due to the stability of the benzyl group to a variety of reaction conditions and the ease with which the benzyl group can be removed.[4] In particular, benzyloxyacetic acid **2** and 4-methoxybenzyl acetic acid **3** have been extensively utilized as synthetically useful intermediates in a wealth of synthetic transformations too numerous to mention (Fig. 1).

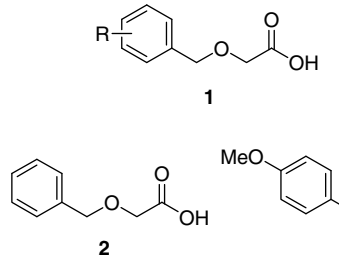
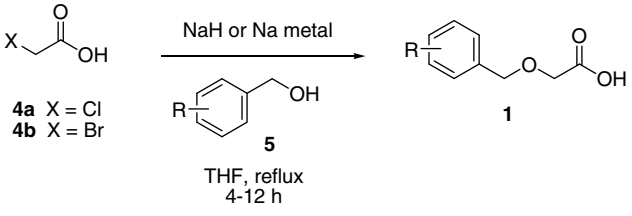


Fig. 1.

The preparation of benzyloxyacetic acids of type **1** has typically relied on the displacement of readily available bromo or chloroacetic acids **4a–b** with a suitably substituted benzyl alcohol **5** (Scheme 1). The most commonly employed base for these transformations is NaH[5] or sodium metal[6] providing the desired products in good to excellent yield. Although the preparation of **2** has been described using sodium metal on a semi-preparative scale, the use of sodium metal, or NaH on a larger scale,[6d] raises serious concerns in terms of safety associated with scale-up due to the pyrophoric nature of NaH and elemental



Scheme 1.

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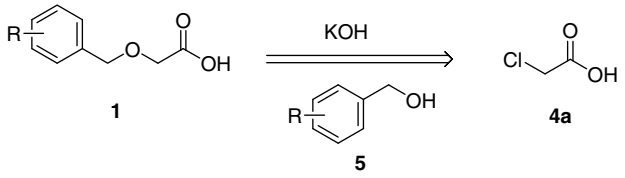
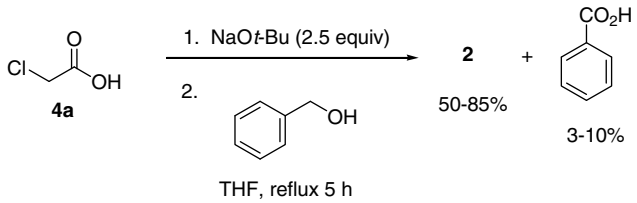
sodium. Issues associated with a rapid release of hydrogen gas upon the deprotonation of both chloroacetic acid and benzyl alcohol render the use of these bases impractical for the large scale development. In addition, the use of these bases requires reaction at elevated temperatures (typically refluxing THF) for prolonged periods of time (4–12 h). Furthermore, these bases are often employed in excess and extreme care must be taken when quenching these reactions.

Benzyloxyacetic acid **2** is commercially available;[7] however, the cost of this valuable reagent is relatively high, presumably due to the available methods for its preparation (NaH or sodium metal) and researchers often resort to preparing this reagent rather than buying it. Recently, we required large quantities of **1** and found that the suitable quantities were unavailable in the required timeframe. Therefore, we elected to investigate alternative and safer methods for the preparation of **2**, which would not only eliminate the safety concerns associated with the use of NaH, but would also be advantageous in terms of overall cost. In this Letter, we document our efforts in this area and outline a practical protocol for the large scale preparation of **1** and related derivatives, which employs powdered KOH as the base (Scheme 2).

Initial efforts were focused on the use of Na *t*-OBu or Na *t*-pentoxide as the base (Scheme 3).[8] The reaction of chloroacetic acid with benzyl alcohol in the presence of 2.5 equiv of Na *t*-OBu resulted in nearly complete conversion to **2**. The analysis of the crude reaction mixture by HPLC indicated that **2** was obtained in HPLC assay yields[9] up to 80%. Also detected in the crude reaction was benzoic acid (5%). Unfortunately, this procedure proved to be non-reproducible and the yield fluctuated between 50% and 85% and varying amounts of benzoic acid (3–10%) were observed. Other bases were examined and the results are summarized in Table 1. When Na *t*-pentoxide served as the base under the identical reaction conditions, benzoic acid was the major reaction product (75%) and the HPLC assay yield of **2** was only 20%. The formation of benzoic acid in each of these reactions was surprising. Control experiments using NaH under standard literature conditions revealed that benzoic acid was formed in up to 2%. We speculate that the attack of **6** onto the carbonyl of the sodium carboxylate of chloroacetic acid **7** leads to the reversible formation of **8** (Scheme 4). Intramolecular hydrogen abstraction can occur resulting in collapse of **8** leading to benzaldehyde **9**, sodium acetate, and NaCl. Benzaldehyde then undergoes a Cannizzaro reaction to



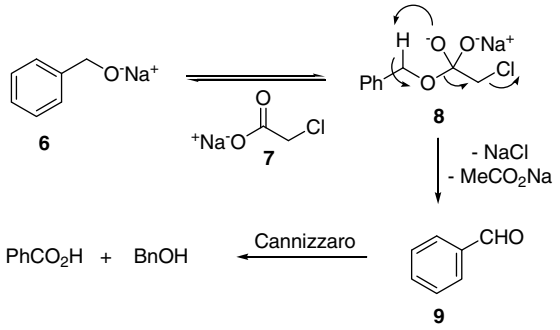
Scheme 2.



Scheme 3.

Table 1

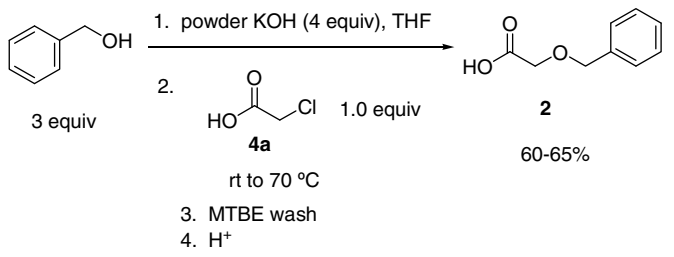
Entry	Base (equiv)	Ratio 4a/BnOH	2 (Yield %)	$PhCO_2H$ (Yield %)
1	Na *t*-pentoxide (4.5)	1:1.2	20	75
2	NaOEt (4.5)	1:1.2	<5	ND
3	NaH (2.5)	1:2	87	1–2
4	5 N NaOH (2.5)	1:5	<5	ND
5	50% NaOH (2.5)	1:4.6	30	1
6	85% KOH (3.5)	1:2.5	40	<1
7	85% KOH (3.0)	1:4.0	65	<1



Scheme 4.

give benzoic acid and regenerate BnOH. The use of NaOEt[10] was also examined, but was found to produce **2** in <5% HPLC assay yield. Since benzoic acid can play a role in the subsequent transformations, its formation needed to be minimized and these approaches were abandoned.

With these results in hand, efforts turned to the use of hydroxide as the base (Table 1).[11] The use of 5 N NaOH (4–5 equiv, THF or 2-MeTHF, 70–80°C, 3–10 h) provided small amounts of **2** (<5%) when allowed to react in the presence of an excess of benzyl alcohol (2–5 equiv) and either bromo or chloroacetic acid (1 equiv). In each case, significant amounts of chloro or bromoacetic acid were observed at the end of the reaction. The use of 50 wt % NaOH proved to be better; however, the isolated yields were typically low (30%). Suspecting that the presence of water may be detrimental to the reaction, the use of commercially available powdered KOH (85%)[12] was examined. The reaction of **4a** with 2.5 equiv of benzyl alcohol and 3.5 equiv of powdered KOH provided **2** in 40% assay yield. The reaction was optimized in terms of benzyl alcohol and KOH charges, reaction time, and temperature. The optimal conditions involved the treatment of a solution of benzyl



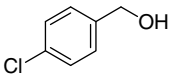
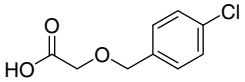
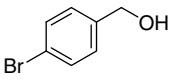
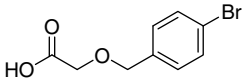
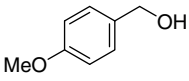
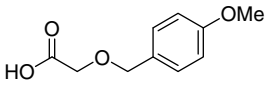
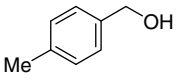
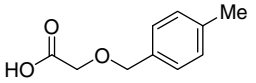
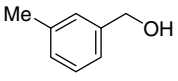
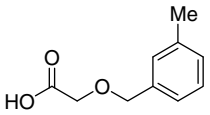
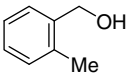
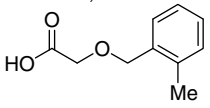
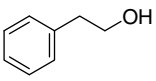
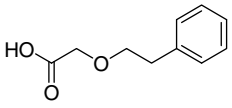
Scheme 5.

alcohol (4 equiv) in THF with solid KOH (3 equiv) followed by the addition of **4a** (1 equiv) and heating to 70°C for 1.5 h (Scheme 5). After an extractive workup to remove excess benzyl alcohol, benzyloxyacetic acid **2** was routinely isolated in 60–65% isolated yield.[13] The isolated product was sufficiently pure for use in subsequent transformations without the need for further purification by either chromatography or distillation. The formation of benzoic acid under these conditions was greatly minimized and was only detected in trace levels (<1%).[14] We assume that the mass balance of the reaction was the conversion of chloroacetic acid to glycolic acid, but conclusive evidence was not rigorously determined. It was also discovered that the reaction proceeded at rt; however, these reactions never approached completion and HPLC assay yields were typically much lower (20–30%) than when the reaction was heated to 70 °C for 1.5 h. The reaction performed equally well with bromoacetic acid and **2** was obtained in similar yields and purity.

The extractive workup employed in the purification of **2** involved a series of MTBE washes to completely remove benzyl alcohol from the aqueous layer.[13] These organic washes containing benzyl alcohol were combined and the benzyl alcohol was recycled to improve the overall efficiency of the process. For example, the solvent was removed under reduced pressure while azeotropically drying the recovered benzyl alcohol. HPLC analysis confirmed the recovery of ~3 equiv of benzyl alcohol from the initial reaction. The crude benzyl alcohol was re-dissolved in dry THF and re-subjected to the optimized reaction conditions described above providing **2** in 60% yield. The recycling of the benzyl alcohol is particularly important if it is expensive or not commercially available. This not only decreases the overall cost, but also further reduces waste making the process greener.

The reaction sequence whereby an appropriately substituted benzyl alcohol (4 equiv) was allowed to react with chloroacetic acid in the presence of powdered KOH (3 equiv) was general, providing an array of substituted benzyloxyacetic acids as outlined in Table 2. Both electron poor (entries 1 and 2) and electron rich (entries 3–6) benzyl alcohols perform equally as well. In addition, phenethyl alcohols (entry 7) are also able to serve as suitable starting materials in this transformation. The preparation of **13** is also noteworthy as **13** has been shown to be a potent inhibitor of hemoglobin S (HbS) gelation and has been extensively studied as a potential antisickling agent.[15] Interestingly, the formation of the corresponding benzoic acid derivatives were observed in certain cases (entries 1, 4, and 6). Attempts to completely suppress the formation of these benzoic acids were unsuccessful; however, when the product was crystalline, recrystallization of the product provided the pure benzyloxyacetic acid derivative without recourse to chromatography.

Table 2

Entry	alcohol	Benzyloxyacetic acid
1	 **10**	 **11**, 74%[a]
2	 **12**	 **13**, 62%
3	 **14**	 **15**, 59%
4	 **16**	 **17**, 46%
5	 **18**	 **19**, 50%[b]
6	 **20**	 **21**, 66%[c]
7	 **22**	 **23**, 64%

[a] 3% of 4-chlorobenzoic acid was present.
[b] 5% of 3-methylbenzoic acid was present.
[c] 5% of 2-methylbenzoic acid was present.

In conclusion, we have outlined an efficient and practical method for the preparation of benzyloxyacetic acids. This procedure provides a safer protocol by eliminating pyrophoric bases such as NaH and sodium metal, which can be conducted on kilogram scale, and requires no chromatography or distillation. Where the substituted benzyl alcohol is either expensive or not commercially available, it can be effectively recycled providing additional benefits in terms of environmental impact and cost.

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7. Benzyloxyacetic acid **2** is commercially available from Aldrich Chemical Co.
8. For a procedure describing the use of NaO–*t*Bu in the preparation of benzyloxyacetic acid, see: Meurs, J. H. H.; De Jong, F. U.S. Patent 5,378,797, 1995.
9. HPLC assay yield refers to quantitative HPLC analysis of reaction mixtures using an analytically pure standard.
10. The use of NaOEt for this transformation has been reported, but acceptable results were not obtained in our hands, see: Kovač, V.; Rapić, V.; Sušnik, I.; Šuprina, M. *J. Organomet. Chem.* **1997**, *530*, 149–158.
11. The use of NaOH for the preparation of **2** has been reported to occur in 86% yield; however, no experimental details were provided, see: Solladie, G.; Hutt, J. *Tetrahedron Lett.* **1987**, *28*, 797–800; See also: Ishiwata, A.; Sakamoto, S.; Noda, T.; Hirama, M. *Synlett* **1999**, 692–694.
12. 85% Powdered KOH is available from Fluka and was used as received.
13. General procedure for the preparation of **2**: In a 3 L, 4 necked round-bottomed flask equipped with a condenser, thermocouple, nitrogen inlet, and mechanical stirrer were added 459 g (4.23 mol) of benzyl alcohol and 500 mL of THF. To the homogeneous solution was added 210 g (3.18 mol) of 85% KOH portion-wise in four 52.5 g aliquots over 4 h while maintaining the internal temperature <40 °C. The bright orange slurry was cooled to 10 °C in an acetone/ice bath and 100 g (1.06 mol) of chloroacetic acid **4a** was added over 35 min in four 25 g aliquots. The solution was heated to 70 °C and stirred for 1.5 h. The mixture was cooled to rt and 400 mL of water and 400 mL of MTBE were added. The layers were separated and the aqueous layer was washed with MTBE (4 × 400 mL). The HPLC analysis of the organic extracts indicated the presence of 330 g (3.04 mol) of BnOH. The aqueous layer was acidified with 250 mL of concentrated hydrochloric acid and extracted with MTBE (2 × 400 mL). The organic extracts were concentrated under reduced pressure to afford 130.1 g (65%) of **2** which was sufficiently pure for use in the subsequent reactions without any further purification.
14. Complete degassing of the reaction mixture has no effect on the level of benzoic acid formed, lending further support for the proposed mechanism in Scheme 4.
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