Tetrahedron 74 (2018) 4236–4241

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Chemoselective reduction of aldehydes and ketones by potassium diisobutyl-*t*-butoxy aluminum hydride (PDBBA)

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ARTICLE INFO

Article history:
Received 31 March 2018
Received in revised form
18 June 2018
Accepted 19 June 2018
Available online 21 June 2018

Keywords:
Chemoselectivity
Reduction
PDBBA
Aldehyde
Ketone

ABSTRACT

t-Butoxy derivatives of DIBALH [lithium diisobutyl-*t*-butoxyaluminum hydride (LDBBA), sodium diisobutyl-*t*-butoxyaluminum hydride (SDBBA), and potassium diisobutyl-*t*-butoxyaluminum hydride (PDBBA)] were examined as chemoselective reducing agents of carbonyl compounds. Among them, PDBBA was found to be the most efficient for the reduction of aldehydes and ketones to the corresponding alcohols in the presence of ester, amide, and nitrile substituents at ambient temperature. In addition, the optimal conditions gave higher chemoselectivity for aldehydes in the presence of ketones.

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1. Introduction

Reductions are fundamental and the most frequently used chemical transformations in organic synthesis [1]. Since the invention of hydride reducing agents for functional groups like carbonyl derivatives, there has been significant progress in the development and identification of novel efficient reagents from the perspectives of chemo- and stereoselectivities [1d-i]. The ready availability of mild and efficient reducing agents that show good selectivity towards multifunctional target molecules [2] is also an important aspect of basic research and development studies. To address these issues, a wide range of reducing agents has been designed and reported by numerous research institutions and academies over many decades [3].

The highly chemoselective reduction of aldehydes and ketones over other carbonyl compounds has been reported widely. For example, although lithium aluminum hydride ($LiAlH_4$) [4] is an extremely powerful reducing agent for most organic functional groups, it gives with no selectivity. On the other hand, sodium borohydride ($NaBH_4$) [5] is a typical cheap and selective reducing agent for aldehydes, ketones, and acyl chlorides. Sodium borohydride at low temperature (−78 °C) [6], with additive (excess Na_2CO_3) [7], resin (Dowex1-x8) [8], and in polyethylene glycol dimethyl ether (PEGDME) [9], have been reported for selective reduction of aldehydes. Generally, $NaBH_4$ reductions involve protic solvents such as methanol, ethanol, or mixed polar solvents for solubility and (or) selectivity [5b,10].

DIBALH is an electrophilic reducing agent known for the reduction of ester and nitriles to aldehydes; it can also reduce most carbonyl derivatives efficiently [11]. Lithium pyrrolidinoborohydride ($LipyrrBH_3$) can selectively reduce only aldehydes and ketones in the presence of nitriles at higher temperatures [12]. Chemoselective reduction of aldehydes and ketones over acyl chlorides and esters using $LiAlH_4$ and silica chloride has been reported [13]. We have previously reported that potassium diisobutyl-*t*-butoxyaluminum hydride (PDBBA) can be used for the chemoselective partial reduction of esters to aldehydes in the presence of nitriles [14].

Several other chemoselective reducing agents of aldehydes over ketones, including lithium tri-*t*-butoxyaluminum hydride (LTBA)/$NaBH_4$ [15], borohydride exchange resin (BER) [16], potassium triacetoxyborohydride ($KBH(OAc)_3$) [17] and zinc borohydride $Zn(BH_4)_2$ [18]. can also be used. However, some of the reported methods involve longer reaction times, high temperature, or the use of additives in large excess.

Despite the considerable progress achieved in the past few decades, there is a growing interest in identifying novel and eco-friendly chemoselective reducing agents. As part of our ongoing

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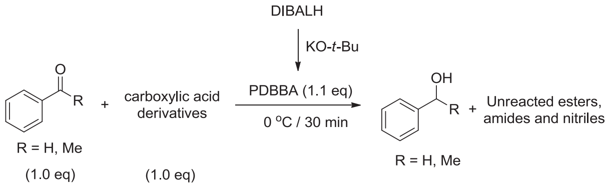
https://doi.org/10.1016/j.tet.2018.06.048
0040-4020/© 2018 Published by Elsevier Ltd.



Scheme 1. Chemoselective reduction of aldehydes and ketones.

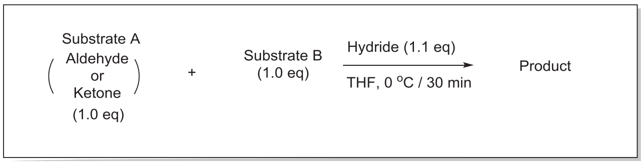
research, we have identified and reported [19] several efficient reducing agents *via* the simple modification of commercial reagents. Herein, we report the chemoselective reduction of aldehydes and ketones using PDBBA, easily prepared by the reaction of DIBAL-H with potassium *t*-butoxide (Scheme 1).

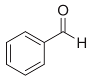
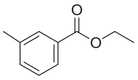
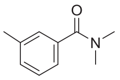
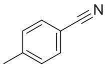
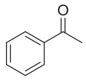
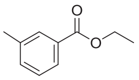
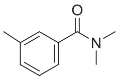
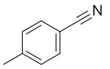
2. Results and discussion

2.1. Evaluation of chemoselective reduction with various reducing agents

First, we screened the chemoselective reducing properties of the *t*-butoxy derivatives of DIBALH, such as lithium diisobutyl-*t*-butoxyaluminum hydride (LDBBA), sodium diisobutyl-*t*-butoxyaluminum hydride (SDBBA), and PDBBA, and compared the results with those obtained with commercial DIBALH and Red-Al. Accordingly, aldehydes and ketones were reduced in the presence of ester, amide, and nitrile functionalities. The results in Table 1 suggest that aldehydes and ketones were reduced to the corresponding alcohols with all the DIBALH-based reducing agents tested (LDBBA, SDBBA and PDBBA). On the other hand, DIBALH itself and Red-Al showed poor selectivity. LDBBA and SDBBA showed relatively good selectivity for the reduction of aldehyde and ketone groups over ester groups; however, ester groups were still reduced by 12% and 8%, respectively. PDBBA showed the best chemoselectivity towards stoichiometric conversion to the desired product among the DIBALH-based reducing agents tested.

Table 1
Evaluation of reducing agents for the chemoselective reduction of aldehydes and ketones.



Entry	Substrate		Hydride	Yield (%)[a]	
	A	B		Substrate A	Substrate B
				S.M / ROH	S.M / RCHO / ROH
1			DIBALH	0 / 85	95 / 0 / 4
			Red-Al	0 / 100	91 / 0 / 8
			LDBBA	0 / 98	87 / 0 / 12
			SDBBA	0 / 99	90 / 0 / 8
			PDBBA	0 / 98	99 / 0 / 0
2			DIBALH	60 / 37	61 / 31 / 5
			Red-Al	0 / 92	63 / 21 / 15
			LDBBA	0 / 100	100 / 0 / 0
			SDBBA	0 / 99	99 / 0 / 0
			PDBBA	0 / 99	99 / 0 / 0
3			DIBALH	0 / 91	98 / 0 / 0
			Red-Al	0 / 97	81 / 18 / 0
			LDBBA	0 / 99	100 / 0 / 0
			SDBBA	0 / 99	99 / 0 / 0
			PDBBA	0 / 100	99 / 0 / 0
4			DIBALH	0 / 99	92 / 2 / 0
			Red-Al	0 / 97	65 / 0 / 34
			LDBBA	0 / 100	86 / 0 / 13
			SDBBA	0 / 100	96 / 0 / 4
			PDBBA	0 / 100	99 / 0 / 0
5			DIBALH	40 / 59	69 / 0 / 28
			Red-Al	0 / 97	65 / 33 / 0
			LDBBA	0 / 97	97 / 0 / 0
			SDBBA	0 / 98	98 / 0 / 0
			PDBBA	0 / 100	100 / 0 / 0
6			DIBALH	0 / 88	93 / 0 / 0
			Red-Al	0 / 97	68 / 31 / 0
			LDBBA	0 / 99	100 / 0 / 0
			SDBBA	0 / 99	98 / 0 / 0
			PDBBA	0 / 98	100 / 0 / 0

[a] Yields were determined by GC using authentic samples.

2.2. Chemoselective reduction of aldehydes and ketones over carboxylic acid derivatives

Based on the results shown in Table 1, we chose PDBBA for functional group screening studies. Accordingly, a series of aldehydes and ketones (aromatic, aliphatic, and conjugated) was treated with PDBBA in the presence of ester, amide, and nitrile functional groups. Table 2 shows that excellent conversion was achieved for all the studied aldehydes and ketones to the corresponding alcohols at ambient temperature. A high degree of chemoselectivity was achieved with both aromatic and aliphatic functional groups. Further, conjugated aldehydes and ketones also smoothly underwent selective reduction with PDBBA (entries 1–14 in Table 2).

Next, the chemoselective reduction of aldehydes and ketones was performed in multifunctionalized compounds (Table 3). Accordingly, substrates containing ester, amide, and nitrile moieties along with aldehydes or ketones were reduced using PDBBA under optimized conditions (0 °C, 30 min). As expected, the aldehydes and ketones furnished the corresponding primary and secondary alcohols with good yields (88–94%) in the presence of other tested functional groups (entries 1–6 in Table 3). An α,β-unsaturated ketone having an ester moiety, ethyl (*E*)-4-oxo-4-phenylbut-2-enoate was treated with PDBBA. This reaction results in formation of a mixture of products which upon purification leads only to the isolation of the major product 4-oxo-4-phenylbut-2-enoate in 55% yield (entry 7 in Table 3). For 4-oxopentanoate, the corresponding lactone was produced after reduction followed by *in situ* cyclization in 68% yield (entry 8 in Table 3).

2.3. Chemoselective reduction of aldehydes over ketones

Under optimized conditions, aldehydes and ketones were reduced chemoselectively using PDBBA in the presence of ester, tertiary amide, and nitrile functional groups with good to excellent conversion at 0 °C for 30 min (by GC). Next, we probed the chemoselective reduction of aldehydes in the presence of ketones. Accordingly, benzaldehyde (1 mmol) and acetophenone (1 mmol) were treated with PDBBA under the optimized conditions. However, we could not obtain significant selectivity for the reduction of the aldehyde over the ketone under these conditions (a 1:1 ratio of primary and secondary alcohols was obtained). Therefore, further optimization was required to achieve better selectivity. We assumed that the reduction of the aldehyde in the presence of the ketone was mainly influenced by the temperature and solvent. To confirm this, we performed a model reaction using benzaldehyde (1 mmol) and acetophenone (1 mmol) with PDBBA for 30 min at −78 °C. From the ^{1}H NMR spectra, it was observed that, even at −78 °C with 5 mL THF, the reduction furnished primary and secondary alcohols in 84% and 11% yields, respectively.

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