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Lithium Bromide as a Flexible, Mild, and Recyclable Reagent for Solvent-Free Cannizzaro, Tishchenko, and Meerwein–Ponndorf–Verley Reactions

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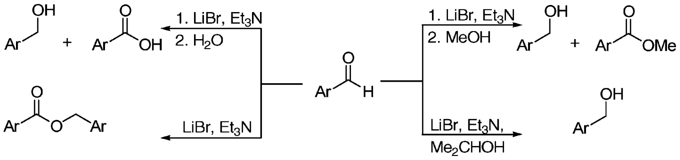
ABSTRACT



A room temperature convenient disproportionation or reduction of aldehydes prompted by lithium bromide and triethylamine is described in a solvent-free environment. Distribution of the products to selectively direct the process toward Cannizzaro or Tishchenko reactions is controlled by the type of workup selection. The presence of hydrogen donor alcohols in the mixture completely diverts the process toward the Meerwein–Ponndorf–Verley reaction.

With increasing global environmental concerns, design of green processes with no use of hazardous and expensive solvents, e.g., “solvent-free” reactions, has gained special attention from synthetic organic chemists.[1] As a result, many reactions are newly found to proceed cleanly and efficiently in the solid state or under solvent-free conditions.[2] Less chemical pollution, lower expenses, and easier procedures are the main reasons for the recent increase in the popularity of solvent-free reactions.

The classical Cannizzaro reaction involves the red-ox conversion of aldehydes into their respective alcohols and carboxylic acids.[3] For many decades, the reaction was generally conducted under strong basic conditions or at elevated temperatures,[4] and is in competition with other parallel carbonyl group transformations. Two of the most closely related processes to the Cannizzaro reaction[5] are the Tishchenko dimerization[6] of aldehydes to form the corresponding ester compounds and the Meerwein−Ponndorf−Verley (MPV)[7] reduction of carbonyl moieties to produce their analogous alcohols. Both reactions are usually conducted under the influence of stoichiometric or excessive amounts of trivalent aluminum-based catalysts.[8] Recent developments in this area involve the use of various Lewis

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[1] (a) Tanaka, K. *Solvent-Free Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2003. (b) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025−1074.

[2] For some recent examples of solvent-free reactions see: (a) Zhao, J. L.; Liu, L.; Sui, Y.; Liu, Y. L.; Wang, D.; Chen, Y. J. *Org. Lett.* **2006**, *8*, 6127−6130. (b) Castrica, L.; Fringuelli, F.; Gregoli, L.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2006**, *71*, 9536−9539. (c) Azizi, N.; Aryanasab, F.; Saidi, M. R. *Org. Lett.* **2006**, *8*, 5275−5277. (d) Lofberg, C.; Grigg, R.; Whittaker, M. A.; Keep, A.; Derrick, A. *J. Org. Chem.* **2006**, *71*, 8023−8027. (e) Hosseini-Sarvari, M.; Sharghi, H. *J. Org. Chem.* **2006**, *71*, 6652−6654. (f) Mojtahedi, M. M.; Abaee, M. S.; Heravi, M. M.; Behbahani, F. K. *Monatsh. Chem.* **2007**, *138*, 95−99. (g) Choudhary, V. R.; Jha, R.; Jana, P. *Green Chem.* **2007**, *9*, 267−272.

[3] (a) Cannizzaro, S. *Justus Liebigs Ann. Chem.* **1853**, *88*, 129−130. (b) For a recent example of Cannizzaro reaction see: Basavaiah, D.; Sharada, D. S.; Veerendhar, A. *Tetrahedron Lett.* **2006**, *47*, 5771−5774.

[4] (a) Maruyama, K.; Murakami, Y.; Yoda, K.; Mashino, T.; Nishinaga, A. *J. Chem. Soc., Chem. Commun.* **1992**, 1617−1618. (b) Jin, S. J.; Arora, P. K.; Sayre, L. M. *J. Org. Chem.* **1990**, *55*, 3011−3018.

[5] Smith, M. B.; March, J. *Advanced Organic Chemistry*; John Wiley & Sons: New York, 2001; pp 1564−1566.

[6] (a) Tischtschenko, W. *J. Russ. Phys. Chem.* **1906**, *38*, 355. (b) Ogata, Y.; Kawasaki, A.; Kishi, I. *Tetrahedron* **1967**, *23*, 825−830.

[7] Meerwein, H.; Schmidt, R. *Justus Liebigs Ann. Chem.* **1925**, *444*, 221−238.

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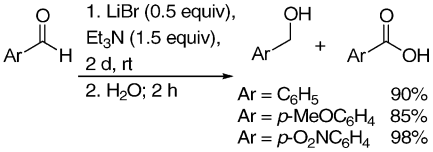
acidic reagents,[9,10] heterogeneous catalytic systems,[11,12] and supercritical solvents.[13,14] Nevertheless, design of new procedures to improve the conditions for these reactions in a milder and less expensive environment would be of interest.

During our recent investigations on Lewis acid-catalyzed carbonyl chemistry,[15] we communicated a room temperature version of the Cannizzaro reaction that could conveniently convert aldehydes to their corresponding alcohols and carboxylic acids under very mild conditions consisting of $MgBr_2 \cdot OEt_2$ and triethylamine (Et_3N).[16] As a consequence of our attempts to apply these mild and convenient conditions to other red-ox reactions of carbonyl compounds, we would like to report a flexible protocol by which selective conversion of aldehydes with no α-hydrogen to their respective alcohols and/or carboxylic functionalities of choice is practically attainable under catalysis of lithium bromide[17] (LiBr) and in the absence of any solvent.

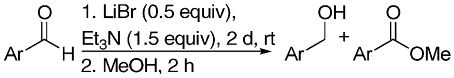
We first optimized the conditions for Cannizzaro reactions of three representative model aldehydes using various quantities of LiBr. The optimum results were obtained by using Et_3N and half equivalents of LiBr when reactions were conducted at room temperature in a solvent-free environment. After complete consumption of the starting aldehydes, treatment of the mixtures with excessive water for about 2 h led to more than 85% formation of the respective alcohols and carboxylic acids (Scheme 1).

Scheme 1



For more convenient fractionation of the reaction mixtures and in order to directly obtain the carboxylic moieties in the form of esters, we replaced water with methanol in the workup procedure. Therefore, when the same reaction mixtures were treated with methanol, respective methyl esters of the starting aldehydes were obtained[18] in excellent amounts along with equivalent quantities of their analogous alcohols (Table 1). After completion of the reactions, LiBr was recovered by a simple filtration and reused efficiently in the next reactions.[19]

Table 1. Cannizzaro Reactions of Aromatic Aldehydes under LiBr Catalysis



entry	products	yield (%)[a]
1	$C_6H_5CH_2OH$; C_6H_5COOMe	97
2	(m-MeO)$C_6H_4CH_2OH$; (m-MeO)C_6H_4COOMe	98
3	(m-F)$C_6H_4CH_2OH$; (m-F)C_6H_4COOMe	98
4	(p-Cl)$C_6H_4CH_2OH$; (p-Cl)C_6H_4COOMe	96
5	β-naphthyl-CH_2OH; β-naphthyl-COOMe	94

[a] Yields of isolated products characterized by ^1H NMR analysis.

Having these promising results in hand, we next decided to extend this chemistry to Tishchenko dimerization of aldehydes as one the most practical tools to synthesize esters and lactones[20] which have many industrial applications[21] as synthetic precursors for durable epoxy resins, dye carriers, solvents, plasticizers, and artificial flavor. The Tishchenko reaction is classically conducted in solution under catalysis of aluminum or magnesium alkoxides, transitional metal complexes,[8a,9a] or rare earth elements.[9b,c] Very recently, Hill and co-workers reported a catalytic Tishchenko reaction for electron deficient aldehydes promoted by alkaline earth metal complexes.[9d]

When we mixed various aldehydes with LiBr and Et_3N under solvent-free conditions at room temperature, formation of dimeric esters of the starting substrates was observed in high yields as represented in Table 2. Notably, the conditions employed here were the same as those used for the Cannizzaro reactions in Scheme 1 except that the aqueous

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(8) (a) Seki, T.; Nakajo, T.; Onaka, M. *Chem. Lett.* **2006**, *35*, 824−829. (b) Cha, J. S. *Org. Process Res. Dev.* **2006**, *10*, 1032−1053. (c) Campbell, E. J.; Zhou, H.; Nguyen, S. T. *Org. Lett.* **2001**, *3*, 2391−2393 and references therein.

(9) (a) Ogata, Y.; Kawasaki, A. *Tetrahedron* **1969**, *25*, 929−955. (b) Burgstein, M. R.; Berberich, H.; Roesky, P. W. *Chem. Eur. J.* **2001**, *7*, 3078−3085. (c) Suzuki, T.; Yamada, T.; Matsuo, T.; Watanabe, K.; Katoh, T. *Synlett* **2005**, 1450−1452. (d) Crimmin, M. R.; Barrett, G. M.; Hill, M. S.; Procopiou, P. A. *Org. Lett.* **2007**, *9*, 331−333.

(10) (a) Boronat, M.; Corma, A.; Renz, M. *J. Phys. Chem. B* **2006**, *110*, 21168−21174. (b) Zhu, Y.; Liu, S.; Jaenicke, S.; Chuah, G. *Catal. Today* **2004**, *97*, 249−255.

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(12) (a) Zapilko, C.; Liang, Y.; Nerdal, W.; Anwander, R. *Chem. Eur. J.* **2007**, *13*, 3169−3176. (b) Samuel, P. P.; Shylesh, S.; Singh, A. P. *J. Mol. Catal. A*: *Chem.* **2007**, *266*, 11−20.

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(15) (a) Abaee, M. S.; Mojtahedi, M. M.; Zahedi, M. M. *Synlett* **2005**, 2317−2320. (b) Mojtahedi, M. M.; Abaee, M. S.; Abbasi, H. *Can. J. Chem.* **2006**, 429−432. (c) Mojtahedi, M. M.; Abaee, M. S.; Abbasi, H. *J. Iran. Chem. Soc.* **2006**, *3*, 93−96. (d) Abaee, M. S.; Mojtahedi, M. M.; Zahedi, M. M.; Sharifi, R. *Heteroatom. Chem.* **2007**, *18*, 44−49.

(16) Abaee, M. S.; Sharifi, R.; Mojtahedi, M. M. *Org. Lett.* **2005**, *7*, 5893−5895.

(17) For some recent synthetic applications of LiBr see: (a) Chakraborti, A. K.; Rudrawar, S.; Kondaskar, A. *Eur. J. Org. Chem.* **2004**, 3597−3600. (b) Maiti, G.; Kundu, P.; Guin, C. *Tetrahedron Lett.* **2003**, *44*, 2757−2758. (c) Roy, S. C.; Guin, C.; Maiti, G. *Tetrahedron Lett.* **2001**, *42*, 9253−9255. (d) Rudrawar, S. *Synlett* **2005**, 1197−1198 and references cited therein.

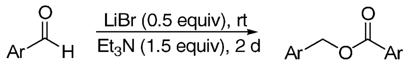
(18) To the best of our knowledge, direct synthesis of nondimeric esters via disproportionation of aldehydes is only reported in intramolecular reactions of aryl glyoxals. For a recent example see: Curini, M.; Epifano, F.; Genovese, S.; Marcotullio, M. C.; Rosati, O. *Org. Lett.* **2005**, *7*, 1331−1333.

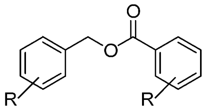
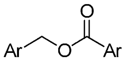
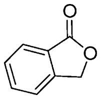
(19) Upon completion of each reaction, the mixture was diluted by toluene and LiBr was separated by filtration. The separated LiBr was washed with toluene, dried under vacuum, and used in the next reactions without significant loss of activity. For further details see the Supporting Information.

(20) (a) Ooi, T.; Ohmatsu, K.; Sasaki, K.; Miura, T.; Maruoka, K. *Tetrahedron Lett.* **2003**, *44*, 3191−3193. (b) Seki, T.; Hattori, H. *Chem. Commun.* **2001**, 2510−2511.

(21) *Ulmann's Encyclopedia of Industrial Chemistry*; Gerhartz, W., Ed.; Wiley-VCH: Weinheim, Germany, 1985; Vol. A9, pp 565−585.

Table 2. Tishchenko Reactions of Aromatic Aldehydes under LiBr Catalysis

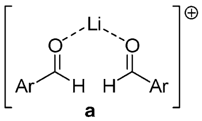


entry	product		yield(%)[a]
1		R=H	96
2		R=*m*-Me	81
3		R=*m*-OMe	95
4		R=*p*-Cl	85
5		R=*p*-Br	80
6		R=*m*-F	97
7		Ar=pyridin-3-yl	80
8		Ar=thiophen-2-yl	66
9		Ar =β-naphthyl	92
10			96

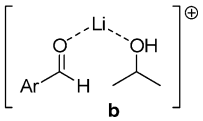
[a] Yields of isolated esters characterized by GC-MS and ^{1}H NMR.

workup was avoided and the products were obtained by simple filtration of the solid fraction and removal of the volatile portions of the mixtures.[19]

This fact that both reactions proceed under the 2:1 ratio of aldehyde:LiBr suggests the presence of a possible reacting species consisting of two aldehyde molecules coordinated through their carbonyl oxygen atoms to the lithium ion (**a**).



a

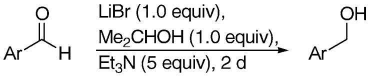


b

Such a reacting species which form a six-membered transition state could facilitate "intramolecular" hydride transfer between the two aldehydes and has been previously reported in the literature for Cannizzaro and Tishchenko reactions.[9a,16]

On the basis of this mechanism, we envisaged that substitution of one of the two reacting aldehydes in the discrete complex by a hydride donor alcohol could divert the process toward the MPV reaction (via **b**), which is usually conducted under aluminum[8b,c] or other metal alkoxides catalysis.[22] Recent advancements to the MPV reaction still involve the use of other basic reagents and catalysts.[8b] Our experiments showed that when 1:1:1 mixtures of LiBr:Me$_2$CHOH:aldehydes were mixed in the absence of any solvent, quantitative reduction of the aldehydes to their respective alcohols was observed (Table 3).[19]

Table 3. MPV Reactions of Aromatic Aldehydes under LiBr Catalysis



entry	product	yield (%)[a]
1	$C_6H_5CH_2OH$	98
2	(m-Me)$C_6H_4CH_2OH$	97
3	(m-MeO)$C_6H_4CH_2OH$	95
4	(m-F)$C_6H_4CH_2OH$	98
5	(p-Cl)$C_6H_4CH_2OH$	99
6	(p-Br)$C_6H_4CH_2OH$	97
7	thiophene-2-yl-CH_2OH	98
8	pyridine-2-yl-CH_2OH	97
9	*trans*-$C_6H_5CH{=}CHCH_2OH$	98

[a] Yields of isolated alcohols characterized by GC-MS and ^{1}H NMR.

In summary, we demonstrated that LiBr, a very stable and mild reagent to handle, can selectively and efficiently direct aldehydes to undergo Cannizzaro, Tishchenko, or MPV reactions with use of very inexpensive solvent-free conditions at room temperature. Recycling of the catalyst and environmental safety of the process are additional advantages of the present method. Attempts to apply these mild conditions to transesterification of esters are currently under investigation.

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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