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Room-Temperature Cannizzaro Reaction under Mild Conditions Facilitated by Magnesium Bromide Ethyl Etherate and Triethylamine[†]

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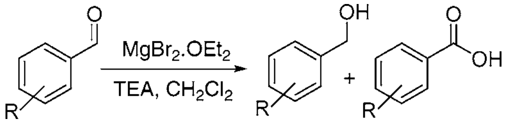
ABSTRACT



A room-temperature convenient Cannizzaro reaction prompted by magnesium bromide ethyl etherate and triethylamine is described for smooth conversion of aromatic aldehydes into their respective alcohols and carboxylic acids. The methodology is applicable to both inter- and intramolecular reactions and could be directed to obtain the carboxylic moiety in the form of an acid, an amide, or an ester compound depending on the selected reaction conditions or workup procedure.

The redox disproportionative conversion of aldehydes into their corresponding alcohols and carboxylic acids, known as Cannizzaro reaction,[1] is one of the oldest processes in synthetic organic chemistry and is classicaly conducted at elevated temperatures using equimolar or excessive amounts of alkali metal hydroxides or other strong bases. Such harsh conditions and competitive formation of undesired side products have been the main limitations for Cannizzaro reaction in the past several decades.[2] Many developments have been made to the original version of the reaction in the past several years by means of microwave irradiation,[3] ultrasound mediation,[4] cation templates,[5] solid-supported reagents,[6] solvent-free conditions,[7] crossed Cannizzaro version of the reaction,[3b,6] gas-phase process,[8] photo induction,[9] and Lewis acid catalysis.[10] Despite all of these modifications, the reaction still requires drastic conditions in most cases. In a few examples conducted at room temperature, strong basic media are still required[7] or yields of the majority of the reactions are rather low or moderate.[10c] During our recent studies on Lewis acid catalyzed aldol reactions of heterocyclic ketones,[11] we realized that in the presence of magnesium bromide ethyl etherate ($MgBr_2{\cdot}OEt_2$) aromatic

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[†] Dedicated to Professor Dale E. Ward.

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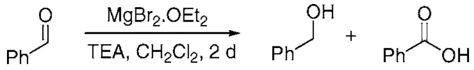
aldehydes could convert to their respective alcohols under certain conditions. Based on these observations and in continuation of our previous experiences with the use of mild Lewis acidic conditions,[12] we would like to herein report a room-temperature protocol for facile inter- and intramolecular Cannizzaro reactions that smoothly transform aldehydes into alcohols and carboxylic acids under very mild conditions using $MgBr_2{\cdot}OEt_2$ and triethylamine (TEA).

Initially, we optimized the intermolecular Cannizzaro reaction of benzaldehyde using various sets of conditions at room temperature as shown in Table 1.

Table 1. Optimization of Cannizzaro Reaction of Benzaldehyde Using $MgBr_2{\cdot}OEt_2$ and TEA

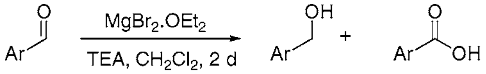


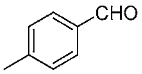
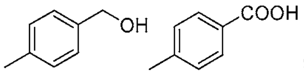
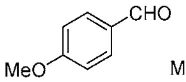
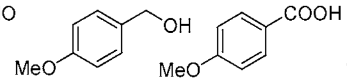
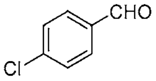
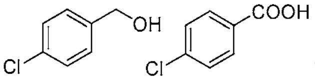
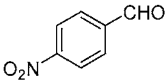
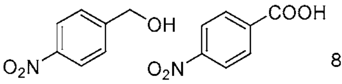
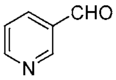
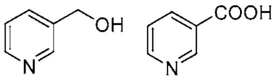
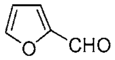
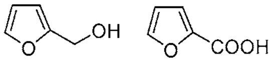
entry	$MgBr_2.OEt_2$ (equiv)	TEA (equiv)	solvent	conversion[a] (%)
1	1.0	2.0	THF	49
2	1.0	2.0	$C_6H_5CH_3$	37
3	1.0	2.0	CH_3CN	85
4	1.0	2.0	CH_3CN	73[b]
5	1.0	2.0	CH_2Cl_2	98
6	1.0	1.5	CH_2Cl_2	61
7	1.0	1.0	CH_2Cl_2	34
8	1.0	0.0	CH_2Cl_2	nr
9	0.5	2.0	CH_2Cl_2	98
10	0.5	2.0	CH_2Cl_2	81[c]
11	0.2	2.0	CH_2Cl_2	55
12	0.1	2.0	CH_2Cl_2	30
13	0.0	2.0	CH_2Cl_2	nr

[a] GC yields. [b] This reaction was conducted under reflux for 3 h. Formation of 23% ester **3d** was also observed. [c] This reaction was conducted under reflux for 12 h. Formation of 15% ester **3d** was also observed.

These results showed that the reaction progress is much more facile in noncoordinating solvents. The best results were obtained when reactions were conducted at room temperature using a 1.0:0.5:2.0 mixture of aldehyde, $MgBr_2{\cdot}OEt_2$, and TEA in dichloromethane (conditions used at entry 9). The generality of the methodology was demonstrated by subjecting various aromatic aldehydes to undergo Cannizzaro reaction under the optimized conditions as illustrated in Table 2.

Table 2. Cannizzaro Reaction of Aromatic Aldehydes under Optimized Conditions



substrate	products	%yield[a]
		91
		85
		88
		85[b]
		82
		90

[a] Yields of isolated alcohols characterized by GC−MS and ^1H NMR. GC data show almost similar yields for carboxylic acids. [b] The reaction was complete in 24 h.

As shown in Table 1, parallel experiments using 1.0 and 0.5 equiv of $MgBr_2{\cdot}OEt_2$ (entries 5 and 9) showed both reactions reach completion in the same periods of time, suggesting that the reacting species might consist of two aldehyde molecules coordinated to magnesium bromide (Figure 1).[13] Such reacting species (**1**) could then undergo nucleophilic attack by TEA to form **2** followed by a hydride transfer from one binding aldehyde to another one, leading to formation of benzyloxy magnesium bromide and unstable amide **3a**, which upon aqueous workup convert to benzyl alcohol and benzoic acid. This hypothesis was supported by obtaining amide **3b** or ester **3c** when diethylamine was used instead of TEA or the workup was carried out by excessive amounts of methanol instead of water.[14]

Extension of the methodology to intramolecular systems using dialdehydes was successfully developed in the next step. In comparison with intermolecular Cannizzaro reaction, the intramolecular counterpart[5,10a,c,15] is of more synthetic value since it could convert each starting dialdehyde into a single α-hydroxy acid. This feature is particularly important for Cannizzaro reaction of aryl glyoxals as an efficient pathway for the synthesis of many biologically active structures such as homatropine,[16] β-lactams,[17] and prostag-

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[13] A rather slow recovery cycle of the catalyst could be suggested on the basis of the results of entries 11 and 12 (Table 1). Completion of the reactions under such conditions takes much longer time than 2 days.

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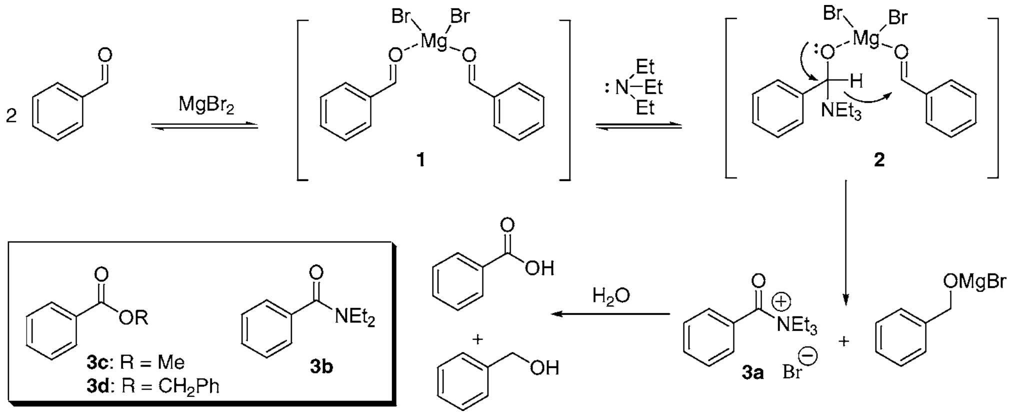
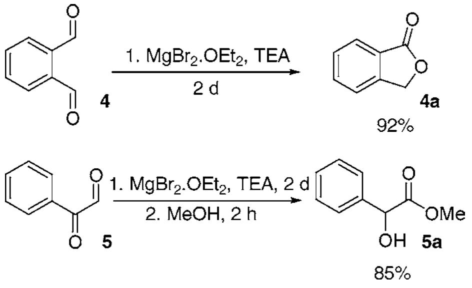


Figure 1. Possible mechanism for $MgBr_2{\cdot}OEt_2$-catalyzed Cannizzaro reaction.

landins.[18] As illustrated in Scheme 1, treatment of *o*-phenylaldehyde (**4**) or phenylglyoxal (**5**)[19] with $MgBr_2{\cdot}OEt_2$ and TEA resulted in facile formation of 3*H*-isobenzofuran-1-one (**4a**) and α-hydroxy-phenylacetic acid methyl ester (**5a**), respectively.

Scheme 1. Intramolecular Cannizzaro Reactions Catalyzed by $MgBr_2.OEt_2$ and TEA in CH_2Cl_2



In conclusion, we disclose the first general method for room-temperature Cannizzaro reactions of aldehydes with no α-hydrogen under $MgBr_2{\cdot}OEt_2$ catalysis. The reactions are very mild, the reagents are fairly inexpensive, conversion rates are high, formation of side products that are normally observed under other conditions is not detected, and use of strong bases or acids during the reaction or at workup are avoided. In addition, the methodology is applicable to both inter- and intramolecular cases and could be directed to obtain products in different functional group status depending on the workup conditions. Attempts for direct disproportionation of aldehydes into amines and amides and study of the chemoselectivity of the methodology in substituted 1,2-dialdehydes are currently under investigation.

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Supporting Information Available: Experimental procedures, spectral data of the products, and results for similar reactions in the presence of other Lewis acids. This material is available free of charge via the Internet at http://pubs.acs.org.

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[19] Compound **5** was used in the form of monohydrate.