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Organo-base mediated Cannizzaro reaction

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Abstract—The organo-base, 1,1,3,3-tetramethylguanidine, mediates the Cannizzaro reaction of reactive aromatic aldehydes in water thus providing the corresponding alcohols and acids. Application of formaldehyde as a sacrificial aldehyde for the cross-Cannizzaro reaction is also presented.

The emerging trends in organic chemistry demand the development of organic reactions/processes catalyzed/mediated by organic molecules and, in fact, several highly enantioselective organo-catalytic reactions have been developed in recent years.[1] The Cannizzaro reaction is one of the oldest and interesting organic reactions involving the base induced disproportionation of an aldehyde devoid of α-hydrogens, to the corresponding primary alcohol and carboxylic acid, thus essentially involving both oxidation and reduction reactions,[2] and still continues to attract the attention of chemists due to its interesting mechanistic and synthetic challenges.[3] Several mechanistic studies[4] have been carried out on this reaction, which usually takes place using strong alkali in aqueous or alcoholic solution, alkali amides in liquid ammonia, metal alkoxides in alcoholic solution or in suspension in inert solvents.[2d] Very recently, an interesting and convenient Cannizzaro reaction mediated by magnesium bromide–ethyl etherate, and triethylamine was reported.[3a] Although many aspects like intramolecular,[3c,5,6] asymmetric,[7] Lewis acid catalyzed,[6] metal/salt mediated/catalyzed,[3a,b,8] solvent-free[9] and microwave induced Cannizzaro reactions[9b,10] are known in the literature, to the best of our knowledge, there is no report on the Cannizzaro reaction mediated by an organo-base alone. We herein report the 1,1,3,3-tetramethylguanidine (TMG) induced Cannizzaro reaction of reactive aromatic aldehydes, which we serendipitously uncovered during our ongoing research program on Baylis–Hillman chemistry.[11]

During our attempts to perform the Baylis–Hillman reaction between the reactive electrophile, pyridine-4-carboxaldehyde **1a** and the less reactive activated alkene, phenyl vinyl sulfoxide **2**,[12] in dioxane/water[13] in the presence of TMG,[14] we did not observe any Baylis–Hillman reaction. However, we obtained pyridin-4-ylmethanol **3a** in 27% yield and were able to recover unreacted phenyl vinyl sulfoxide **2** in 47% yield. We also noticed the formation of 1-phenylsulfinyl-2-(pyridin-4-ylmethoxy)ethane **4**, in 10% yield (contaminated with ≈5–10% impurities) (Scheme 1).

Compound **3a** may have been formed via the Cannizzaro reaction of **1a** and the formation of **4** may be attributed to a Michael-type addition of pyridin-4-ylmethanol **3a** (which was generated in situ) to phenyl vinyl sulfoxide. We were able to prepare **4** in a separate experiment via the reaction of pyridin-4-ylmethanol **3a** with phenyl vinyl sulfoxide **2** and confirmed the structure from spectral data (IR, ^{1}H and ^{13}C NMR) (Scheme 2).[15]

Thus, **1a** does not undergo the Baylis–Hillman reaction with phenyl vinyl sulfoxide in the presence of TMG in water, but instead undergoes a Cannizzaro reaction. The reaction between **1a** and TMG in water, in the absence of phenyl vinyl sulfoxide also resulted in the formation of the corresponding alcohol **3a**. The best result was obtained when a mixture of pyridine-4-carboxaldehyde **1a** (2 mM) and TMG (2 mM) in water (0.5 mL) was kept at room temperature for 5 h, providing pyridin-4-ylmethanol **3a** in 40% isolated yield, after work-up followed by column chromatography (silica gel, EtOAc) (Table 1, entry 1).[16] This was an encouraging result in the sense that this is the first example of an organo-base (TMG) induced Cannizzaro reaction. We

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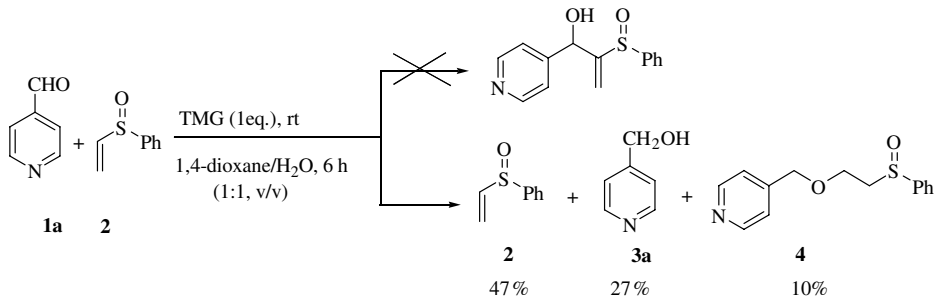
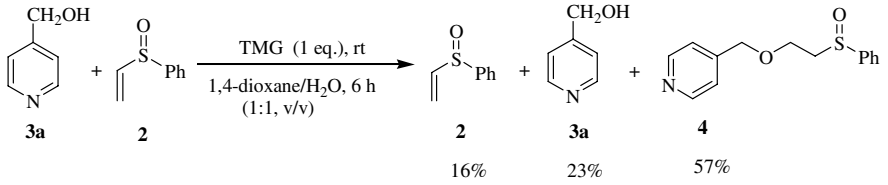
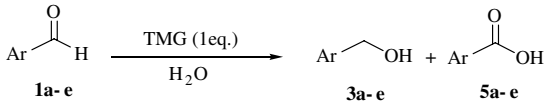


Scheme 1. Treatment of pyridine-4-carboxaldehyde with phenyl vinyl sulfoxide in the presence of TMG in dioxane–water.



Scheme 2. Reaction of pyridine-4-ylmethanol with phenyl vinyl sulfoxide in the presence of TMG.

Table 1. TMG-induced Cannizzaro reaction[a,17]



Entry	Substrate	Ar	Time (h)	Product yield[b,c] (%)	
				Alcohol[d]	Acid[d]
1	**1a**	Pyridin-4-yl	5	40 (**3a**)	35 (**5a**)
2	**1b**	Pyridin-3-yl	7	44 (**3b**)	41 (**5b**)
3	**1c**	Pyridin-2-yl	7	39 (**3c**)	36 (**5c**)
4	**1d**	4-$(NO_2)C_6H_4$	10	30 (**3d**)	27 (**5d**)
5	**1e**	3-$(NO_2)C_6H_4$	20	26 (**3e**)	23 (**5e**)
6	**1d**	4-$(NO_2)C_6H_4$	0.5[e]	36 (**3d**)	42 (**5d**)
7	**1e**	3-$(NO_2)C_6H_4$	3[e]	38 (**3e**)	30 (**5e**)
8	**1e**	3-$(NO_2)C_6H_4$	10[e]	42 (**3e**)	43 (**5e**)
9	**1f**	C_6H_5	20[f]	≈2%	

[a] The Cannizzaro reactions were carried out on 2 mM of aldehyde (**1a**–**e**) using 1,1,3,3-tetramethylguanidine (2 mM) in water (0.5 mL) at room temperature.

[b] Products **3b**, **c** and **3e** were obtained as liquids and **3a**, **d** and **5a**–**e** were obtained as crystalline solids.

[c] All the products gave satisfactory IR, ^{1}H NMR (200 or 400 MHz) and ^{13}C NMR (50 or 100 MHz) spectral data.

[d] Isolated yields of the pure products [for **3a**–**c** after column chromatography (silica gel, 100% EtOAc), for **3d**, **e** after column chromatography (silica gel, 20% EtOAc in hexanes), for **5a**, **b** after crystallization from water, for **5c** after crystallization from $CHCl_3$ and for **5d**, **e** after crystallization from ethyl acetate–hexanes (1:4)].

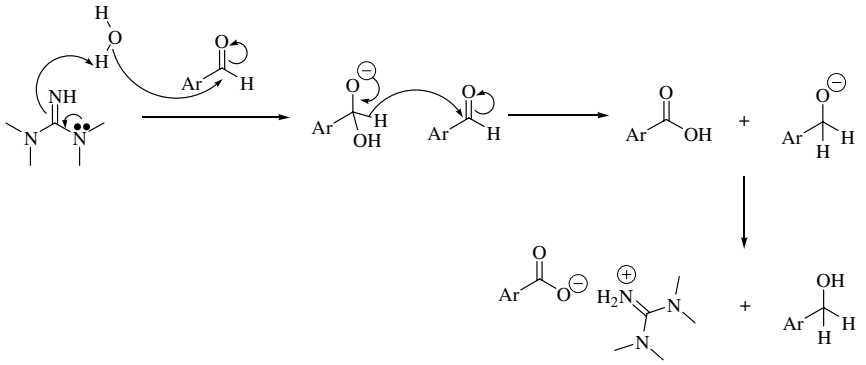
[e] These reactions were also carried out on 2 mM of aldehyde (**1d**–**e**) using 1,1,3,3-tetramethylguanidine (2 mM) in water (0.5 mL) at 100 °C.

[f] This reaction was carried out at 100 °C.

found that other tertiary amines such as DABCO, DBU, and 3-hydroxyquinuclidine were less effective[18] to perform the Cannizzaro reaction with pyridine-4-carboxaldehyde under similar conditions.

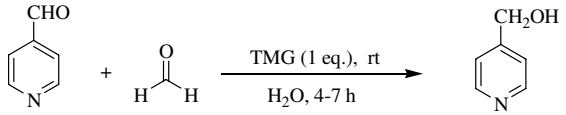
We extended this strategy to other reactive aldehydes such as pyridine-3-carboxaldehyde **1b**, pyridine-2-carboxaldehyde **1c**, and 4- and 3-nitrobenzaldehydes (**1d** and **1e**) to provide the corresponding alcohols (**3b**–**e**) in 26–44% isolated yields (Table 1, entries 2–5). We also isolated the oxidized products (acids **5a**–**e**) in 23–41% yields (Table 1, entries 1–5). Since the reactions were reasonably slow in the case of 4- and 3-nitrobenzaldehydes at room temperature we carried out the reactions at 100 °C and obtained the corresponding alcohols (36% and 42%) and acids (42% and 43%) at a faster rate (Table 1, entries 6 and 8). Cannizzaro reaction of less reactive aldehydes such as benzaldehyde was very very slow, even after refluxing for 20 h, only a very small amount (≈2%) of benzyl alcohol was formed (as indicated by a singlet at δ 4.7 in the ^{1}H NMR spectrum of the crude product) (Table 1, entry 9).

Based on the above observations, a plausible mechanism is presented in Scheme 3 for the TMG-mediated Cannizzaro reaction. As is well known, the Cannizzaro reaction provides the reduced product (alcohol) and the oxidized product (acid) in a maximum of 50% (theoretical) yield from the corresponding aldehyde. Formaldehyde has been successfully employed as a sacrificial aldehyde in the cross-Cannizzaro reaction so that the other and more important aldehyde has the opportunity to be converted into the corresponding alcohol in high yield.[2d,9b] To examine this aspect we selected pyridine-4-carboxaldehyde **1a** as a representative case and carried out the reaction with HCHO in the presence of TMG in water. Thus, treatment of pyridine-4-carboxaldehyde **1a** (2 mM) with formalin (37% w/v) (2 mM) in water (0.5 mL) in the presence of 1,1,3,3-tetramethylguanidine (2 mM) at room temperature for 4 h, provided the desired alcohol **3a** in 50% isolated yield. In order to optimize the reaction conditions, we also carried out the cross-Cannizzaro reaction of **1a**, with various amounts



Scheme 3. Plausible mechanism for the Cannizzaro reaction.

Table 2. Formation of pyridin-4-ylmethanol **3a** via the cross-Cannizzaro reaction[a,b]



1a **3a**

Entry	HCHO (equiv)	Time (h)	Yield[c] (**3a**) (%)
1	1	4	50
2	2	4	56
3	4	4	60
4	8	4	60
5	16	7	64

[a] All the reactions were carried out on 2 mM of aldehyde **1a** using 1,1,3,3-tetramethylguanidine (2 mM) in water (0.5 mL) at room temperature.

[b] The alcohol was obtained in all the cases as a colorless solid and gave satisfactory IR, ^{1}H NMR (200 or 400 MHz) and ^{13}C NMR (50 or 100 MHz) spectral data.

[c] Isolated yields of the pure alcohol after column chromatography (silica gel, 100% EtOAc).

of HCHO and found that a maximum yield (64%) of the desired alcohol **3a** could be obtained with 16 equiv of HCHO (Table 2, entry 5).

In conclusion, we have described for the first time an organo-base (TMG) promoted Cannizzaro reaction. Although this reaction is applicable only to reactive aromatic aldehydes, this work provides new perspectives and avenues for further understanding the applications of the Cannizzaro reaction.

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15. Spectral data of 1-phenylsulfinyl-2-(pyridin-4-ylmethoxy)ethane **4**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.98–3.15 (m, 2H), 3.75–3.86 (m, 1H), 3.96–4.09 (m, 1H), 4.53 and 4.61 (ABq, $J = 13.6$ Hz, 2H), 7.23 (d, $J = 5.6$ Hz, 2H), 7.47–7.57 (m, 3H), 7.64–7.70 (m, 2H), 8.58 (d, $J = 5.6$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 57.69, 63.39, 71.32, 121.53, 123.69, 129.18, 130.97, 143.63, 146.59, 149.60; IR (neat): ν 1604, 1109, 1045 cm^{-1}; LC–MS (m/z): 262 $(M+H)^+$.
16. Typical experimental procedure: Cannizzaro reaction of pyridine-4-carboxaldehyde: Pyridin-4-ylmethanol **3a**: A solution of pyridine-4-carboxaldehyde **1a** (0.214 g, 2 mM) and 1,1,3,3-tetramethylguanidine (0.23 g, 2 mM) in water (0.5 mL) was kept at room temperature for 5 h. The reaction mixture was diluted with $CHCl_3$ (5 mL) and an aqueous solution of K_2CO_3 (0.552 g in 1 mL of H_2O). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (4×40 mL). The combined organic layer was dried over anhydrous sodium sulfate (Na_2SO_4). The solvent was evaporated and the crude product thus obtained, was purified by column chromatography (silica gel, 100% EtOAc) to afford **3a** (0.087 g, 40%) as a colorless solid {theoretical yield, 50% (0.109 g)}. Mp: 55–57 °C (lit.[17] 57–60 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.78 (br s, 1H), 4.74 (s, 2H), 7.30 (d, $J = 5.6$ Hz, 2H), 8.52 (d, $J = 5.6$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 62.69, 121.32, 148.99, 151.71; IR (KBr): ν 3375 cm^{-1}.

Pyridine-4-carboxylic acid (**5a**): To the aqueous solution (obtained from the above reaction mixture), concd HCl was added slowly to adjust the pH of the solution to 3.6 (iso-electric point of pyridine-4-carboxylic acid) and the solution then cooled to ~5–6 °C. The solid thus obtained was recrystallized from water to provide pure pyridine-4-carboxylic acid **5a** (0.086 g, 35% yield) as a white crystalline solid. Mp: 306 °C (lit.[17] 315 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.78–7.88 (m, 2H), 8.74–8.82 (m, 2H), 13.67 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 122.75, 138.09, 150.59, 166.18; IR (neat): ν 3000–2600, 1718 cm^{-1}.
17. Compounds **3a**–**e** and **5a**–**e** are reported in *Dictionary of Organic Compounds*, 4th ed.; Pollock, J. R. A., Stevens, R. Eds.; Eyre & Spottiswoode: London, 1980; for **3a**, **3b** and **3c** see Vol. 5, pp 2819; for **3d** and **3e** see Vol. 4, pp 2439; for **5a** see Vol. 5, pp 2817; for **5b** and **5c** see Vol. 5, pp 2816; for **5d** and **5e** see Vol. 4, pp 2436 and 2435, respectively.
18. In the case of DABCO and 3-hydroxyquinuclidine we noticed less than 5% formation of pyridin-4-ylmethanol (**3a**) while there is $\approx$ 25% formation of **3a** with DBU.