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gem-Dibromomethylarenes: A Convenient Substitute for Noncommercial Aldehydes in the Knoevenagel−Doebner Reaction for the Synthesis of α,β-Unsaturated Carboxylic Acids

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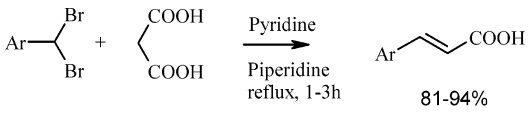

A facile synthesis of α,β-unsaturated carboxylic acids from *gem*-dibromomethylarenes is described. *gem*-Dibromomethylarenes are employed for the first time in the Knoevenagel−Doebner reaction as aldehyde equivalents for the efficient synthesis of α,β-unsaturated carboxylic acids.

α,β-Unsaturated carboxylic acids compose a relatively large family of organic acids, which are important reagents in organic synthesis both as intermediates and final products. For example, they have been used to prepare compounds of biological relevance such as terahydromyricoid[1] or the antibacterial reutericyclin.[2] Also, they are present in some natural products (e.g., the secretion of juice of honeybee queen[3] and caffeic acid[4]) and are versatile building blocks in organic synthesis. For their application in the food industry, polymer industry, perfume industry, medicine, and technical applications, they are synthesized on a commercial scale. Of the various methods, the Knoevenagel−Doebner reaction is widely recognized as the leading method to access the carbon−carbon double bond necessary to provide the α,β-unsaturated carboxylic acid.[5]

Though the Knoevenagel−Doebner reaction has been extensively documented, substitution of the aldehyde component with an alternative functional group has not been documented. Therefore, the development of a simple and stable substitute for these aromatic aldehydes by using inexpensive and readily available reagents would extend the scope of the Knoevenagel−Doebner reaction in organic synthesis. Recently, *gem*-dihalomethylarenes have received considerable attention due to their application in the preparation of aldehydes.[6] To our knowledge, the use of *gem*-dihalomethylarenes is limited to the synthesis of aldehydes and there is no literature on their use to synthesize α,β-unsaturated carboxylic acids. In this Note, we report a new, rapid, and efficient method for the Knoevenagel−Doebner reaction via the reaction between a *gem*-dibromomethylarene (as a substitute for aldehyde) and an active methylene compound such as malonic acid, thus providing access to α,β-unsaturated carboxylic acids.

The synthetic approach started from the commercially available benzal bromide. A mixture of benzal bromide **1a** (1.0 equiv) and malonic acid (2.0 equiv) with anhydrous pyridine in the presence of a catalytic quantity (0.04 equiv) of piperidine was stirred at reflux. The starting material was consumed in 1.5 h as indicated by TLC analysis. After workup and purification by crystallization, cinnamic acid **2a** was isolated in 93% yield. Use of 2 equiv of malonic acid was found to be optimal for the complete conversion of **1a** to **2a**. Screening of various base catalysts such as triethylamine, *N*-ethyldiisopropylamine, DBU, DABCO, pyrrolidine, and morpholine was carried out. While pyrrolidine and morpholine catalyzed the reaction to quantitative yields in 2−3 h, the other bases were found to be inefficient in promoting this reaction.

Next, we examined the progress of the reaction by omitting piperidine. When a mixture of benzal bromide and malonic acid was refluxed with anhydrous pyridine in the absence of piperidine, 14 h were required for the reaction to afford 17% of **2a** along with 73% of benzaldehyde after aqueous workup. With a catalytic amount of piperidine, the reaction took barely an hour for completion. Encouraged by this success, the other *gem*-dibromomethylarenes **1b**−**p** were subjected to the Knoevenagel−Doebner reaction with malonic acid to yield the corresponding α,β-unsaturated carboxylic acids in excellent yields. The results are depicted in Table 1.

Herein, we report a general approach to α,β-unsaturated carboxylic acids in high yields by subjecting the easily accessible *gem*-dibromomethylarenes to malonic acid in refluxing pyridine. Benzal bromide is known to produce a fairly stable bis-pyridinium cation on refluxing with pyridine. Kröhnke has shown that the bis-pyridinium cation of benzal bromide is slowly hydrolyzed in water to benzaldehyde and pyridine.[7] As the formation of benzaldehyde was not observed at any stage of the reaction, we speculated a reaction involving nucleophilic catalysis between the bis-cation and malonic acid followed by

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(1) Song, J.; Hesse, M. *Tetrahedron* **1993**, *49*, 6797−6804.
(2) Marquardt, U.; Schmid, D.; Jung, G. *Synlett* **2000**, 1131−1132.
(3) Callow, R. K.; Johnston, N. C. *Bee World* **1960**, *41*, 152−153.
(4) Cho, H.; Ueda, M.; Tamaoka, M.; Hamaguchi, M.; Aisaka, K.; Kiso, Y.; Inoue, T.; Ogino, R.; Tatsuoka, T.; Ishihara, T.; Noguchi, T.; Morita, I.; Murota, S. *J. Med. Chem.* **1991**, *34*, 1503−1505.
(5) (a) Knoevenagel, E. *Ber*. **1898**, *31*, 2596 and 2619. (b) Doebner. O. *Ber*. **1900**, *33*, 2104. (c) Kingsbury, C. A.; Max, G. *J. Org. Chem*. **1978**, *43*, 3131−3139. (d) Mogilaiah, K.; Reddy, G. R. *Synth. Commun.* **2004**, *34*, 2, 205−210. (e) McNulty, J.; Steere, J. A.; Wolf, S. *Tetrahedron Lett.* **1998**, *39*, 44, 8013−8016. (f) Manitto, P.; Monti, D.; Zanzola, S.; Speranza, G. *J. Org. Chem*. **1997**, *62*, 19, 6658−6665. (g) Masuno, M. N.; Pessah, I. N.; Olmstead, M. M.; Molinski, T. F. *J. Med. Chem*. **2006**, *49*, 4497−4511. (h) Tokunaga, N.; Hayashi, T. *Tetrahedron*: *Asymmetry* **2006**, *17*, 607−613. (i) Arun, K. S.; Anuj, S.; Bhupendra, P. J. *Tetrahedron* **2007**, *63*, 960−965 and references cited therein.
(6) (a) Mandal, A. B.; Augustine, J. K.; Quattropani, A.; Bombrun, A. *Tetrahedron Lett.* **2005**, *46*, 6033−6036. (b) Coleman, G. H.; Honeywell, G. E. *Organic Syntheis*; John Wiley and Son: New York, 1943; Collect. Vol. II, pp 89−91.
(7) Kröhnke, F.; Leister. H. *Chem. Ber*,. **1958**, *91*, 1295.

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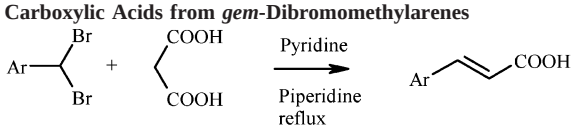
TABLE 1. Synthesis of α,β-Unsaturated Carboxylic Acids from *gem*-Dibromomethylarenes



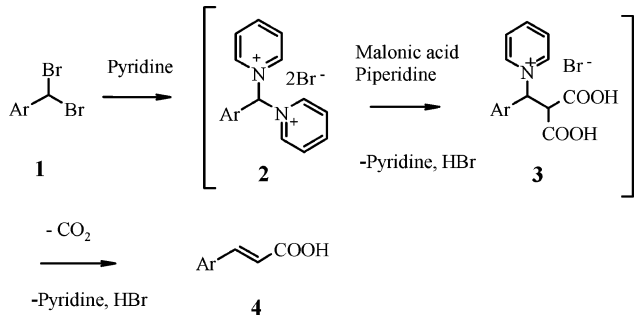
Entry	Substrate[a]	Time (h)	Product	Yield (%)[b]
1	**1a**	1.5	**2a**	93
2	**1b**	2	**2b**	89
3	**1c**	1.5	**2c**	90
4	**1d**	1	**2d**	84
5	**1e**	3	**2e**	87
6	**1f**	1.5	**2f**	91
7	**1g**	2	**2g**	81
8	**1h**	2	**2h**	87
9	**1i**	2	**2i**	92
10	**1j**	3	**2j**	94
11	**1k**	1.5	**2k**	88
12	**1l**	2	**2l**	89
13	**1m**	2	**2m**	91
14	**1n**	3	**2n**	82
15	**1o**	1	**2o**	90
16	**1p**	1.5	**2p**	88

[a] Substrates are prepared from the commercial methyl analogues by readical bromination. [b] Isolated yields.

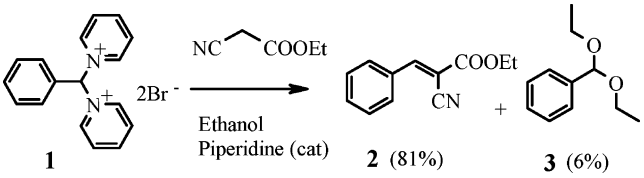
tandem decarboxylation and elimination of pyridine to produce the cinnamic acid (Scheme 1).

The longer reaction time in the absence of piperidine suggests that pyridine is not basic enough to generate the carbon nucleophile from malonic acid. The formation of benzaldehyde when piperidine was omitted is attributed to the hydrolytic cleavage of unreacted bis-pyridinium intermediate during aqueous workup.

SCHEME 1. Proposed Mechanism of the Reaction between *gem*-Dibromomethylarene and Malonic Acid in Pyridine



SCHEME 2



The condensation of benzylpyridinium salts with active methylene compounds in the presence of base is reported.[8] In the light of this information, the reaction was further probed by isolating the bis-pyridinium salt of benzal bromide[9] **1** (Scheme 2). On treating this intermediate with ethyl cyanoacetate in absolute ethanol containing a catalytic amount of piperidine at reflux for 4 h, ethyl-2-cyano-3-phenylacrylate **2** (Scheme 2) was obtained in 81% yield. Benzaldehyde diethylacetal **3** (Scheme 2), resulting from the reaction between ethanol and the bis-cation was also isolated in small quantity.[10]

gem-Dibromomethylarenes being a stable and readily accessible substitute for noncommercial and unstable aldehydes, this transformation would extend the scope of the Knoevenagel−Doebner reaction in organic synthesis. In addition, it is worthy to note that both aromatic and heteroaromatic *gem*-dibromides bearing various functionalities such as carboxylate, amide, halogen, nitro, cyano, boronate, and methoxy groups survived the course of reaction and provided high yields of corresponding α,β-unsaturated carboxylic acids.

In conclusion, we have demonstrated a general methodology wherein *gem*-dibromomethylarenes are employed as aldehyde equivalents for the first time in the Knoevenagel−Doebner reaction for the efficient synthesis of α,β-unsaturated carboxylic acids. As this reaction provides α,β-unsaturated carboxylic acids in a single step from *gem*-dibromomethylarenes, we believe that this transformation would be of potential application in synthetic chemistry.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400-MHz and 100-MHz Bruker spectrometers, respectively. Elemental analysis was performed on a Thermo Finnigan FLASH EA 1112 CHN analyzer. Melting points were recorded (uncorrected) on a Buchi Melting Point B-545 instrument. Compounds described previously in the literature were characterized only by ^{1}H and ^{13}C NMR. All *gem*-dibromomethyl compounds except **1a** were synthesized and purified in house from the corresponding commercially available methyl analogues, using radical bromination at reflux. The methyl analogue 2,2,7-trimethylbenzo[1,3]dioxin-4-one, which was used for the synthesis of **1f**, was prepared according to a known literature method.[11] Substrates **1o** and **1p** were synthesized by treating the commercial boronic acids with pinacol (1.1 equiv) in toluene followed by radical bromination.

Representative Procedure for the Synthesis of α,β-Unsaturated Carboxylic Acids. To a mixture of benzal bromide **1a** (10 g, 0.04 mol) and malonic acid (8.35 g, 0.08 mol) in pyridine (30 mL) was added piperidine (0.14 mL, 0.0016 mol) and the mixture was refluxed for a given period of time (entry 1, Table 1). The completion of reaction was confirmed by TLC. The brown reaction mixture was cooled and poured onto ice containing hydrochloric acid. The solid precipitated was collected by filtration, washed with water (3 × 75 mL), and dried under suction to afford 5.5 g (93%) of cinnamic acid **2a** as a white solid. Alternatively, the reaction mixture could be poured onto water and extracted with ethyl acetate. The organic phase could be evaporated and directly loaded onto a silica gel column. This method is suitable for isolating α,β-unsaturated carboxylic acids obtained from nitrogen heterocycles.

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Supporting Information Available: Experimental procedures and spectroscopic data for all the compounds except **1a** and **2a** described in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Condensation of pyridinium cations with active methylene compounds has been documented but has not been applied to bis-pyridinium cations: Richard H. Kline, US3989738;, Appl. No. 597803, 1976.

(9) A mixture of benzal bromide (10 g, 0.04 mol) and pyridine (7 g, 0.088 mol) in anhydrous acetone (20 mL) was stirred at 70 °C for 12 h under nitrogen atmosphere. The precipitated solid was carefully filtered, washed with acetone, and dried under vacuum to afford 11 g (67%) of the 1,1′-(phenylmethylene)bispyridiniumdibromide **1** (Scheme 2) as yellow solid. The NMR spectral data of this product are provided in the Supporting Information.

(10) It is worthy to note that when 1,1′-(phenylmethylene)bispyridinium dibromide **1** (Scheme 2) was refluxed in absolute ethanol for 6 h, benzaldehyde diethylacetal was obtained in 73% yield.

(11) An analogue is reported by: Deshpande, M S.; Wei, J.; Luo, G.; Cianci, C.; Danetz, S.; Torri, A.; Tiley, L.; Krystal, M.; et al. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 17, 2393−2396.