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Organocatalytic Knoevenagel Condensations by Means of Carbamic Acid Ammonium Salts

Nobuyuki Mase* and Takuya Horibe

Department of Molecular Science, Faculty of Engineering, Shizuoka University, 3-5-1 Johoku, Hamamatsu 432-8561, Japan

tnmase@ipc.shizuoka.ac.jp

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ABSTRACT

The Knoevenagel condensation between an active methylene compound and an aromatic aldehyde with a carbamic acid ammonium salt used as an organocatalyst gave the desired Knoevenagel products in up to 98% yield. The reaction occurred at rt and in a short reaction time under solvent-free conditions. In addition, no extraction, wash, or chromatography steps were needed to obtain a high-purity Knoevenagel product.

Although carbamic acid (H_2NCO_2H) is an unstable compound that has not been isolated yet, it has been detected by low-temperature IR measurements.[1] In contrast, carbamic acid ammonium salts are quite stable compounds.[2] For instance, ammonium carbamate (NH_4^+ $H_2NCO_2^-$), used as a mild ammoniating reagent, is readily prepared by reacting solid carbon dioxide with liquid ammonia.[3] Similarly, the reaction of primary and/or secondary amines **1** with carbon dioxide provides alkyl-substituted ammonium carbamates **3** *via* formation of a weakly acidic and unstable alkylcarbamic acid **2** (Scheme 1).[4,5]

Dimethylammonium dimethylcarbamate (DIMCARB, **3a**, R = Me), which is the only commercially available dialkylammonium carbamate,[6] is well-known to be a useful dimethylamine source for preparative amidation of carboxylic acids, anhydrides, or ester derivatives.[7] In addition, DIMCARB is used as a reagent in the Willgerodt–Kindler synthesis of *N*,*N*-dimethylthiocarboxamides.[8] Due to the increasing awareness of environmental issues, DIMCARB recently attracted attention as a self-associated, distillable ionic medium.[4] Furthermore, this metal-free ammonium salt promotes an aldol condensation through an iminium intermediate (Mannich-type mechanism),[9,10] and as reported by our group, it has been used for protection- and metal-free syntheses of [*n*]-shogaols.[11] Although dialkylammonium carbamates are potentially valuable not only as reagents or reaction media but also as promoters or catalysts, their use in organic synthesis is limited. Here, we report the use of a carbamic acid ammonium salt in Knoevenagel condensations as an easily removable organocatalyst under solvent-free conditions.

The Knoevenagel condensation, discovered by E. Knoevenagel in 1896,[12] is widely used both in the academic environment and in the chemical–pharmaceutical and perfume industries. In general, a secondary amine

(1) Rossi, L. In *Science of Synthesis*; Knight, J., Ed.; Thieme: 2005; Vol. 18, p 461.
(2) Roughton, F. J. W. *J. Am. Chem. Soc.* **1941**, *63*, 2930.
(3) Rossi, L. In *Science of Synthesis*; Knight, J., Ed.; Thieme, 2005; Vol. 18, p 462.
(4) Kreher, U. P.; Rosamilia, A. E.; Raston, C. L.; Scott, J. L.; Strauss, C. R. *Molecules* **2004**, *9*, 387.
(5) Schroth, W.; Schädler, H.-D.; Andersch, J. *Z. Chem.* **1989**, *29*, 129.
(6) Dimethylcarbamic acid, hydrochloride (CAS No. 22055-85-2) and diethylcarbamic acid, and sodium salt (CAS No. 18869-61-9) are other comercially available carbamic acid salts.
(7) Theodoropulos, S. *Eur. Pat. Appl.*, EP 062161, 1982, p 23.
(8) Schroth, W.; Andersch, J. *Synthesis* **1989**, 202.
(9) Kreher, U. P.; Rosamilia, A. E.; Raston, C. L.; Scott, J. L.; Strauss, C. R. *Org. Lett.* **2003**, *5*, 3107.
(10) (a) Chowdari, N. S.; Barbas, C. F., III. *Org. Lett.* **2005**, *7*, 867. (b) Rosamilia, A. E.; Giarrusso, M. A.; Scott, J. L.; Strauss, C. R. *Green Chem.* **2006**, *8*, 1042. (c) Zoto, C. A.; Connors, R. E. *J. Mol. Struct.* **2010**, *982*, 121.
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(12) Knoevenagel, E. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 2345.

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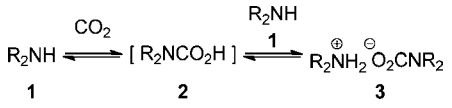
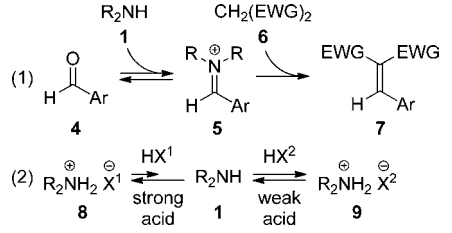
Scheme 1. Formation of Carbamic Acid and Its Salts



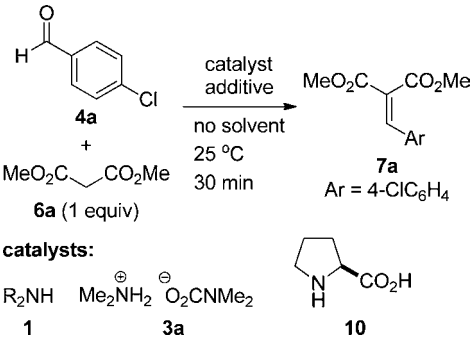
catalyzes the Knoevenagel condensation in the presence of a small amount of an acid such as acetic acid and benzoic acid (commercially available benzaldehyde contains a small amount of benzoic acid),[13] and the reaction can occur through an iminium or aminal (Knoevenagel mechanism, Scheme 2, reaction 1) and/or an ammonium enolate (Hann−Lapworth mechanism).[14] When a pure aldehyde is employed, a small amount of an acid additive should be added.[13b] In fact, the presence of the acid additive could accelerate the Knoevenagel condensations due to the increased electrophilicity of the aldehyde and/or increased leaving-group ability of the amine caused by the enhanced hydrogen bond network. However, in the presence of a strong acid additive the amine **1** is easily converted to its ammonium salt **8** (Scheme 2, reaction 2). Since the nucleophilicity of the ammonium salt **8** is much less than that of the parent amine **1**, heating conditions have been generally employed in order to improve the reactivity. Furthermore, in order to remove the ammonium salt **8** from the reaction mixture, the protocol has been integrated with a solvent extraction step. Thus, we hypothesized that if a very weak acid additive such as carbamic acid **2** and/or its salts **3** are used, the Knoevenagel condensation could be performed at low temperature. In addition, if a volatile amine **1** is employed, due to the instability of the carbamic acid **2** it would be easy to remove the catalyst from the reaction mixture under reduced pressure conditions.

Scheme 2. Secondary Amine Promoted Knoevenagel Condensation



The Knoevenagel condensation of the less reactive dimethyl malonate (**6a**) with 4-chlorobenzaldehyde (**4a**) was adopted as a model reaction to evaluate the catalytic ability of some catalysts. In fact, the acidity of the malonate

Table 1. Knoevenagel Condensations Promoted by Various Catalysts[a]



entry	catalyst	additive	yield (%)[b]
1	**1a** (R = Me)	none	82
2	**1b** (R = -$(CH_2)_5$-)	none	62
3	**1b**	AcOH	11
4	**1b**	$PhCO_2H$	29
5	**10**	none	0
6	**3a**	none	90

[a] Conditions: catalyst (0.5 mmol), additive (if used, 0.5 mmol), **4a** (0.5 mmol), and **6a** (0.5 mmol) at 25 °C for 30 min. [b] Determined by GC analysis using TC-17 column.

6a (pK_a = 15.9) is low compared to that of other molecules such as, for instance, acetylacetone (pK_a = 13.3) and malononitrile (pK_a = 11.1).[15] Dimethylamine (**1a**) and piperidine (**1b**) promoted the Knoevenagel condensation in moderate to good yields (Table 1, entries 1 and 2), but their salts with carboxylic acid resulted in low conversions at 25 °C (entries 3 and 4). Although it is known to promote the Knoevenagel condensation at rt in DMSO in the presence of a natural amino acid,[16] the expected benzylidenemalonate product **7a** was not obtained under solvent-free conditions when L-proline was used as the catalyst (entry 5). On the other hand, the commercially available DIMCARB (**3a**) effectively afforded the product **7a** in 90% yield within 30 min by using only 1.0 equiv of malonate **6a** (entry 6).

Encouraged by these results, we then compared the catalytic ability of various amines **1** and their alkylammonium carbamates **3**, which are not commercially available with the exception of DIMCARB. Thus, various alkylammonium carbamates **3** were prepared by the reaction of primary or secondary amines **1** with supercritical carbon dioxide (50 °C, 10 MPa, 2 h) and stored in a hermetically sealed bottle at rt. Bulky disubstituents (Table 2, entries 1−3) and monosubstituted carbamates (**3**) resulted in low yields of the desired product (**7a**) (entries 4−7). Yet, the yields were improved with the employment of cyclic carbamates, among which piperidinium carbamate (**3b**)

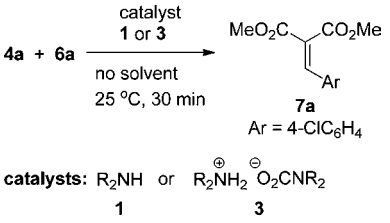
(13) (a) Kuhn, R.; Badstübner, W.; Grundmann, C. *Ber. Dtsch. Chem. Ges.* **1936**, *69*, 98. (b) Allen, C. F. H.; Spangler, F. W. *Org. Synth.* **1945**, *25*, 42. (c) Meltzer, R. I.; Lustgarten, D. M.; Fischman, A. *J. Org. Chem.* **1957**, *22*, 1577.

(14) Hann, A. C. O.; Lapworth, A. *J. Chem. Soc., Trans.* **1904**, *85*, 46.

(15) http://www.chem.wisc.edu/areas/reich/pkatable/index.htm (accessed Feb 20, 2013), Bordwell pK_a Table (Acidity in DMSO).

(16) (a) Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. *Synth. Commun.* **2003**, *33*, 1587. (b) Ramachary, D. B.; Barbas, C. F., III. *Chem.—Eur. J.* **2004**, *10*, 5323.

Table 2. Comparison of Catalytic Ability between Amines **1** and Alkylammonium Carbamates **3**[a]



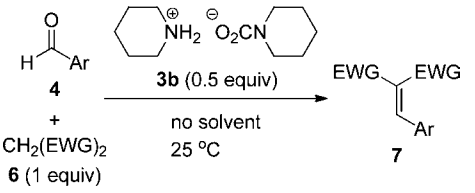
entry	catalyst	R	equivalents of catalyst	yield (%)[b] using **1**	yield (%)[b] using **3**
1	**a**	Me	1.0	82	90
2	**c**	Et	1.0	74	70
3	**d**	*i*-Pr	1.0	0	0
4	**e**	Me, H	1.0	36	17
5	**f**	Pr, H	1.0	24	14
6	**g**	Hexyl, H	1.0	12	8
7	**h**	Bn, H	1.0	22	13
8	**i**	-$(CH_2)_4$-	1.0	67	80
9	**j**	-$(CH_2)_6$-	1.0	56	71
10	**b**	-$(CH_2)_5$-	1.0	62	98
11	**b**	-$(CH_2)_5$-	1.0	62	85[c]
12	**b**	-$(CH_2)_5$-	1.0	62	14[d]
13	**b**	-$(CH_2)_5$-	0.5	40	93
14	**b**	-$(CH_2)_5$-	0.3	30	63
15[e]	**b**	-$(CH_2)_5$-	0.1	9	53
16[f]	**b**	-$(CH_2)_5$-	0.1	–	80[g]
17[f]	**b**	-$(CH_2)_5$-	0.05	–	74[g]

[a] See Table 1, footnote a. [b] See Table 1, footnote b. [c] Catalyst **3b** was prepared in gaseous CO_2 (50 °C, 5 MPa, 2 h). [d] Catalyst **3b** was prepared with atmospheric CO_2 bubbling. [e] The reaction was carried out for 1 h. [f] The reactions were carried out at 70 °C and 1 MPa for 6 h. [g] The catalyst **3b** was *in situ* prepared in autoclave.

efficiently promoted Knoevenagel reactions in up to 98% yield within 30 min (entries 8–10). It is known that carbamates **3** can be prepared by saturating the solutions of the corresponding amines **1** with gaseous carbon dioxide in conventional organic solvents.[3] However, the piperidinium carbamate (**3b**) prepared with atmospheric CO_2 bubbling decreased the chemical yield (entries 10–12). In addition, while the piperidinium carbamate (**3b**) could undergo the Knoevenagel reaction in moderate to good yields at low catalyst concentrations (0.1–0.5 equivalents, entries 13–15), the amount of catalyst highly affected the chemical yield when **4a** and **6a** reacted with free amine **1**. The catalytic activity was improved by preparing the piperidinium carbamate (**3b**) *in situ* at 70 °C and 1 MPa in an autoclave and decreasing the catalyst loading to 0.05 equiv (entries 16 and 17).

The efficiency of the Knoevenagel condensation involving the piperidinium carbamate (**3b**) was examined with a series of arylaldehyde acceptors **4** and active methylene compound donors **6** (Table 3). In most cases, the reactions finished within 30 min, but since semisolid formation has been sometimes observed, stirring was continued for 14–24 h in order to ensure reaction completeness. Knoevenagel reactions of the malonate **6a** with aromatic

Table 3. Scope of Substrates[a]



entry	**4** Ar	**6** EWG	isolated yield (%)[b]	product
1	4-ClC_6H_4	CO_2Me	91	**7a**
2	4-$O_2NC_6H_4$	CO_2Me	84	**7b**
3	3-$O_2NC_6H_4$	CO_2Me	82	**7c**
4	2-$O_2NC_6H_4$	CO_2Me	87	**7d**
5	4-NCC_6H_4	CO_2Me	76	**7e**
6	4-$MeOC_6H_4$	CO_2Me	75	**7f**
7	[c]	CO_2Me	79	**7g**
8	Ph	CO_2Me	93	**7h**
9	1-naphthyl	CO_2Me	68	**7i**
10	2-naphthyl	CO_2Me	83	**7j**
11	4-ClC_6H_4	CO_2Et	80	**7k**
12	4-ClC_6H_4	CO_2Bn	62	**7l**
13	4-ClC_6H_4	COMe	46	**7m**
14	4-ClC_6H_4	CO_2Et, COMe	77 (*E*/*Z* = 7/3)	**7n**
15	4-ClC_6H_4	CO_2Et, CN	63 (*E* only)	**7o**

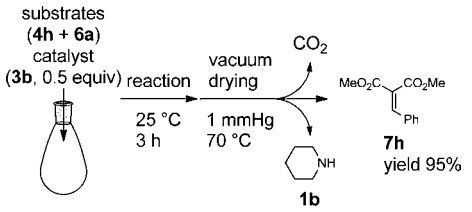
[a] Conditions: catalyst **3b** (0.25 mmol), **4** (0.5 mmol), and **6** (0.5 mmol) at 25 °C for 14–24 h. [b] Isolated yield after SiO_2 column chromatography. [c] Ar = benzo[*d*][1,3]dioxol-5-yl (= piperonal).

aldehydes **4** substituted with both electron withdrawing groups (e.g., chloro, nitro, and cyano groups) and electron donating groups (e.g., methoxy group on the phenyl ring) furnished the desired products **7** in good yields after direct isolation using SiO_2 column chromatography (entries 1–10). Bulky substituents on the ester moiety showed negative effects on the chemical yield (entries 11–12). Since Michael addition of **6m** (EWG = Ac) with the Knoevenagel product **7m** formed *in situ* was observed, the yield of **7m** resulted in a lower value than expected (entry 13). Instead, the reaction between the asymmetrical substrates β-keto ester **6n** and α-cyano ester **6o** afforded (*E*)-isomers as major products (entries 14 and 15).

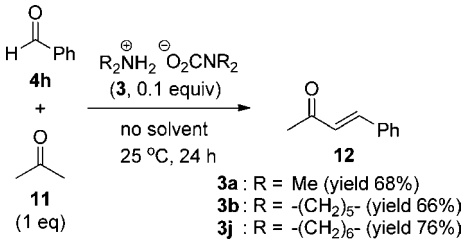
Interestingly, 98.6 wt % of piperidinium carbamate (**3b**) gradually decomposed to form piperidine (**1b**) and carbon dioxide at rt and vaporized from the storage flask in 1 day under reduced pressure (1 mmHg).[17] In order to exploit this physical property, we attempted to develop a practical and easy isolation method. Thus, afterwards the substrates **4h** and **6a** reacted in the presence of the piperidinium carbamate (**3b**) at 25 °C for 3 h, and the reaction mixture was directly evaporated under 1 mmHg at 70 °C in order to remove the catalyst **3b**. The desired Knoevenagel product **7h** was obtained in 95% yield. Since no extraction, washing, or chromatography steps were needed to obtain a high-purity Knoevenagel product, this procedure could

(17) Decomposition of **3b** stored in a hermetically sealed bottle at rt.: 0.2 wt % (6 h), 0.4 wt % (1 day), 0.5 wt % (3 days), and 3 wt % (7 days).

Scheme 3. Easy Isolation of the Knoevenagel Product



Scheme 4. Mannich-Type Condensation Using Alkylammonium Carbamate **3**



be advantageously employed in industrial processes (Scheme 3).

Furthermore, alkylammonium carbamates **3** were tested in the synthesis of an α,β-unsaturated ketone **12** *via* Mannich-type condensation. The less reactive acetone donor **11** was transformed into an enone **12** in good isolated yield (Scheme 4).[9,11] In this context, we found that the seven-membered azepanium carbamate (**3j**) was the most effective among the tested catalysts.

As shown in Figure 1, ionic disassociation of the alkylammonium carbamate **3b** forms the carbamic acid **2b** and the nucleophilic amine **1b**. The aldehyde **4** activated by the carbamic acid **2b** reacts with the amine **1b** to give the iminium cation intermediate **5b** that, in turn, undergoes a Mannich-type condensation with the active methylene compound donors **6**. Subsequent elimination of piperidine (**1b**) from the Mannich adduct **13** is facile and gives the Knoevenagel product **7**.

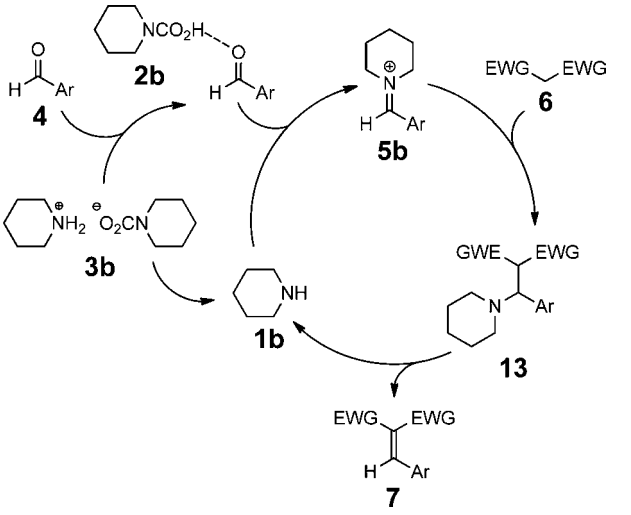


Figure 1. Reaction mechanism.

In summary, we have developed a catalytic Knoevenagel condensation by using the easily removable alkylammonium carbamate as an organocatalyst. This type of reaction can be carried out at rt in a short period of time under solvent-free conditions. In addition, no extraction, washing, or chromatography steps are needed to obtain the Knoevenagel product with excellent purity. Further studies focusing on the full range of these alkylammonium carbamate-promoted reactions are currently under investigation and will be reported as appropriate.

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Supporting Information Available. Experimental procedures, product characterization data, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.