



Solvent-free NbCl₅ catalyzed condensation of 1,3-dicarbonyl compounds and aldehydes: a facile synthesis of trisubstituted alkenes

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ABSTRACT

A simple preparation of trisubstituted alkenes by condensation of β-diketones or β-ketoesters with aldehydes in presence of NbCl₅ as a Lewis acid catalyst in solvent-free conditions is described.

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C–C-bond formation reactions are one of the important reactions in synthesis. The classical Knoevenagel reaction,¹ which is a modification of the Aldol reaction, is a well-known example for C–C-bond formation reaction wherein the end products are generally the trisubstituted alkenes, that is, α,β-unsaturated carbonyl compounds or α,β-unsaturated esters. These adducts are good Michael acceptors and can be used directly in the Diels–Alder reactions for further transformations and thus find wide applications in pharmaceuticals.² Base-promoted Knoevenagel condensation is well known,³ also, the importance of Knoevenagel adducts has led to an exploration of several other reagents to promote Knoevenagel condensation. Examples include protocols involving ionic liquids,⁴ heterogenous catalysts such as clays,⁵ hydrotalcites,⁶ zeolites,⁷ and also acid catalysts such as CeCl₃·7H₂O/NaI,⁸ HClO₄–SiO₂,⁹ TiCl₄,¹⁰ and ZnCl₂.¹¹ Reports are also present wherein high temperatures¹² or microwave irradiation¹³ has been used for this transformation without any catalysts. Very often, prolonged reaction conditions or high temperatures become a barrier, and hence an efficient procedure is always desirable.

The oxophilicity of high valence Nb(V) has enabled it to act as the reagent/catalyst for several Lewis acid-mediated reactions such as the intramolecular oxidation–reduction process,¹⁴ the Diels–Alder reaction,¹⁵ allylation of aldehydes and imines,¹⁶ and complex formations as Lewis acids¹⁷. Our own interest with this metal halide has resulted in achieving organic transformations such as Prins type cyclization,¹⁸ C–H insertion reactions of alpha-diazoesters,¹⁹ synthesis of 3,4-dihydropyrimidinones²⁰ and recently C-, N-, O-, and S-nucleophilic substitution reactions of benzylic alcohols.²¹ In continuation of our investigations with NbCl₅ as a Lewis acid catalyst, we herein report a mild protocol for Knoevenagel condensation (Scheme 1).

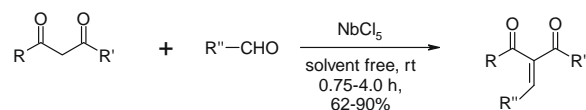
Initially, benzaldehyde was treated with ethyl acetoacetate in the presence of NbCl₅ (10 mol %) in DCM at rt. We found that the

reaction proceeds well within 2 h and results in a single product. This product was isolated and characterized as a trisubstituted olefin. Interestingly, the reaction also worked in the absence of DCM leading only to the desired product. Also, when the efficiency of the catalyst was investigated by studying the reaction with different concentrations (5%, 10%, and 20%), we found that 20 mol % NbCl₅ was the best in terms of yield and duration. Thus, after optimizing the reaction conditions, a few other combinations were tested to evaluate the scope of this transformation (Table 1, entries 1–3). Even the diethyl malanoate (Table 1, entry 4) worked well under the present protocol to yield the trisubstituted olefin in 86% yield.

Gratified with the results obtained from condensation of β-ketoesters and aldehydes, we wondered whether NbCl₅ would facilitate the condensation reaction of β-diketones and aldehydes, since β-diketones are relatively less reactive due to the formation of a stable six-membered enolate.

Towards these studies, the reaction of acetylacetone with benzaldehyde in the presence of 20 mol % NbCl₅ was investigated (Table 1, entry 5). We were delighted to see that the reaction worked well producing the Knoevenagel adduct within 1 h in 85% yield. In contrast, Sambri and co-workers²² recently used magnesium perchlorate for Knoevenagel condensation, and reported that a similar transformation took a longer time (70 h) with 65% yield at room temperature.

Impressed with the result obtained, a few more examples were investigated for the generality of the reaction. Several aromatic and



R = Me, Ph, OEt

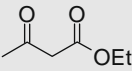
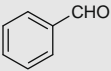
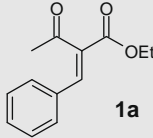
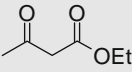
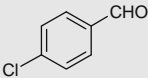
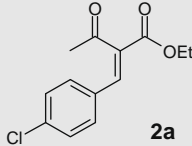
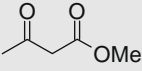
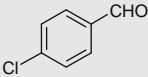
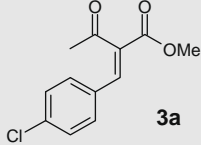
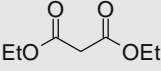
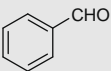
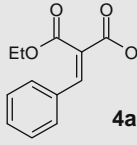
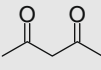
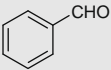
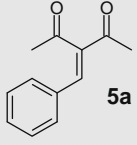
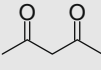
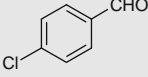
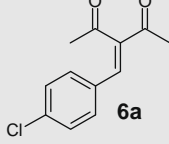
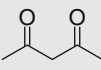
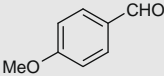
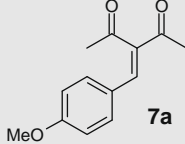
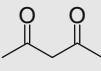
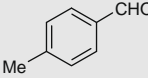
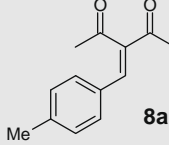
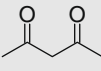
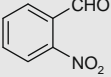
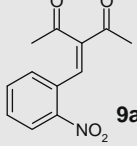
R' = Me, Ph, OEt, OMe

R'' = Ph, n-heptyl, cyclohexyl, pClC₆H₄-, pOMeC₆H₄-, pMeC₆H₄-, oNO₂C₆H₄-

Scheme 1.

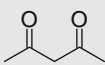
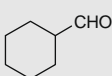
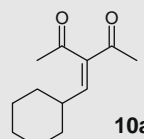
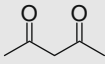
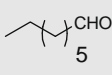
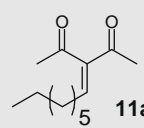
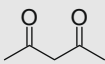
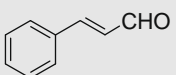
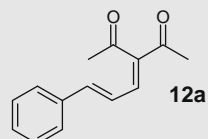
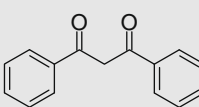
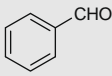
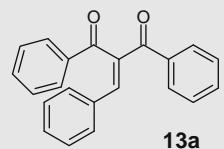
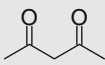
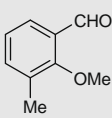
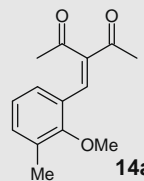
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Table 1
Knoevenagel condensation of β -ketoesters with aromatic aldehydes

Entry	β -Ketoester β -Diketone	Aldehyde	Product ^a	Time (h)	Yield (%)
1			 1a	1.5	73
2			 2a	1.5	80
3			 3a	1.5	80
4			 4a	3.0	86
5			 5a	1.0	85
6			 6a	1.0	84
7			 7a	1.5	80
8			 8a	1.5	78
9			 9a	0.75	90

(continued on next page)

Table 1 (continued)

Entry	β -Ketoester β -Diketone	Aldehyde	Product ^a	Time (h)	Yield (%)
10				4.0	62
11				2.0	70
12				3.0	65
13				1.5	85
14				1.5	87

^a The products were isolated and characterized by ¹H NMR, ¹³C NMR, and mass spectroscopy.

aliphatic aldehydes were treated with β -diketones to yield the corresponding condensation products.²³ It was found that the aliphatic aldehydes took longer time compared to aromatic aldehydes (Table 1, entries 10–12), took longer durations compared to aromatic aldehydes (Table 1, entries 5–9), and that aromatic aldehydes with electron-withdrawing groups (Table 1, entries 6 and 9) afforded slightly higher yields compared to aromatic aldehydes bearing electron-donating groups (Table 1, entries 7 and 8). All the products were isolated and characterized by ¹H NMR, ¹³C NMR, and mass spectroscopy analysis.²⁴

In conclusion, NbCl₅ has been used efficiently to catalyze the condensation reaction between β -diketones/ β -keto esters and aldehydes. A solvent-free reaction with a shorter time and mild reaction conditions involving room temperature and single product formation are the key features involved in the present protocol. These features will enable this protocol to find wide applications in the field of organic synthesis.

Acknowledgments

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Supplementary data

Supplementary data (spectroscopic data of products **1a**, **2a**, **4a**, **6a**, and **8a–14a**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.015.

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23. *General procedure for condensation reaction:* A 1,3-dicarbonyl compound (1 mmol) was taken in a round-bottomed flask and to this was added 1.2 equiv of aldehyde followed by 20 mol % of NbCl₅. The reaction mixture was stirred at rt against the time mentioned in the table. The reaction was quenched by the addition of saturated aq NaHCO₃ solution and the product was extracted with ethylacetate. The product was purified by column chromatography using EtOAc/Hexane as an eluent. As per the comment raised by the referee, a reaction was attempted on 10 mmol scale. Compound **5a** was prepared on 10 mmol scale in 1.5 h with 83% yield using 20 mol % catalyst.
24. *Data of representative examples:* (*E*)-Methyl 2-(4-chlorobenzylidene)-3-oxobutanoate (**3a**): Reddish solid, mp = 80 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.16 (s, 3H), 2.58 (s, 3H), 6.11–6.12 (m, 4H), 6.27 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 26.5, 52.6, 129.1, 130.6, 136.8, 134.5, 140.0, 169.7, 194.3. IR (KBr): 821, 1088, 1250, 1618, 1654, 1733, 2362, 2855, 2932 cm⁻¹. ESIMS: *m/z* 261 (M⁺+Na). HRMS calcd for C₁₂H₁₁O₃NaCl, 261.0294. Found 261.0289. 3-Benzylidenepentane-2, 4-dione (**5a**): Yellow liquid. ¹H NMR (200 MHz, CDCl₃): δ 2.24 (s, 3H), 2.38 (s, 3H), 7.36 (m, 5H), 7.44 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 26.2, 31.3, 128.7, 129.4, 130.4, 132.6, 139.6, 142.5, 196.4, 205.3. IR (neat): 760, 1174, 1245, 1614, 1658, 1708, 2923, 3002 cm⁻¹. ESIMS: *m/z* 211 (M⁺+Na). HRMS calcd for C₁₂H₁₂O₃Na, 211.0734. Found 211.0735. 3-(4-Methoxybenzylidene)pentane-2, 4-dione (**7a**): Yellow liquid. ¹H NMR (300 MHz, CDCl₃): δ 2.28 (s, 3H), 2.26 (s, 3H), 3.83 (s, 3H), 6.87 (d, *J* = 9.0 Hz, 2H), 7.31 (d, *J* = 9.0 Hz, 2H), 7.37 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 26.2, 31.6, 55.3, 114.5, 125.2, 131.6, 139.7, 140.6, 161.6, 196.4, 206.1. IR (neat): 831, 1108, 1174, 1258, 1258, 1513, 1599, 1653, 1706, 2844, 2926, 3004 cm⁻¹. ESIMS: *m/z* 241 (M⁺+Na). HRMS calcd for C₁₃H₁₄O₃Na, 241.0840. Found 241.0833.