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Microwave-accelerated conjugate addition of aldehydes to α,β-unsaturated ketones

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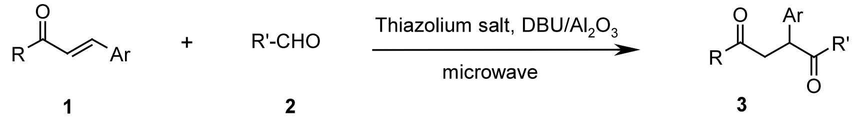
Abstract—Aldehydes undergo smooth conjugate addition to α,β-unsaturated ketones in the presence of 5-(2-hydroxyethyl)-1,3-thiazolium halides and DBU adsorbed onto the surface of basic alumina under microwave irradiation and solvent-free conditions to afford 1,4-diketones in enhanced yields and reduced reaction times compared to conventional methods.

The use of inorganic solid supports as reaction media in organic synthesis is increasingly widespread due to improved efficiency of many surface-bound reagents.[1] Microwave irradiation has become a powerful synthetic tool for the rapid synthesis of a variety of organic compounds.[2] Microwave-assisted reactions have attracted much interest because of the simplicity in operation and milder reaction conditions. The salient features of the microwave approach are improved yields, enhanced reaction rates, formation of pure products in high yields and ease of isolation. Solvent-free microwave assisted reactions have gained more popularity as they provide an opportunity to work with open vessels. This avoids the risk of development of high pressure and provides the possibility of scaling-up the reaction and helps the induction of the reaction under dry conditions.[3]

1,4-Diketones are very useful precursors for the synthesis of a variety of heterocycles such as pyrroles, furans, thiophenes and pyridazines.[4] In addition, they are valuable intermediates in the synthesis of cyclopentenone derivatives and many others.[5] One of the most straightforward synthetic methods for the synthesis of 1,4-diketones is the conjugate addition of aldehydes to α,β-unsaturated ketones employing quaternary thiazolium salts in the presence of a tertiary amine.[6,7] This conventional approach only provides satisfactory results with aliphatic aldehydes. The reactions of aromatic aldehydes with α,β-unsaturated ketones require high temperatures and longer reaction times and also the products are obtained in low to moderate yields. Thus there is scope to develop a rapid and high yielding protocol for the preparation of 1,4-diketones of synthetic importance.

In this report, we describe our results on the microwave-accelerated synthesis of 1,4-diketones using a solid supported reagent system, thiazolium salt–DBU–Al_2O_3. Thus treatment of aliphatic, aromatic and heteroaromatic aldehydes with α,β-unsaturated ketones in the presence of an equimolar ratio of 5-(2-hydroxyethyl)-1,3-thiazolium chloride or bromide and DBU dispersed onto the surface of alumina using microwave irradiation under solvent-free conditions afforded the corresponding γ-diketones in high yields (Scheme 1 and Table 1).



Ar = phenyl, thienyl, pyridyl, furanyl ; R = aryl; R' = aryl, alkyl, heterocyclic, α,β-unsaturated systems

Scheme 1.

Keywords: conjugate addition; α,β-unsaturated ketones; microwave; 1,4-diketones.

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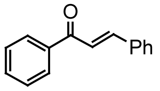
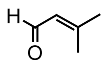
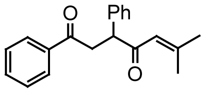
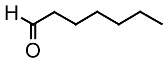
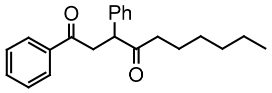
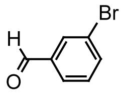
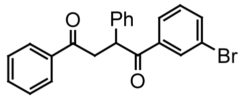
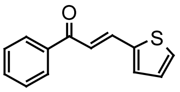
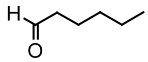
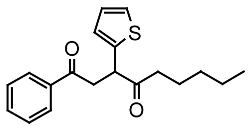
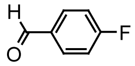
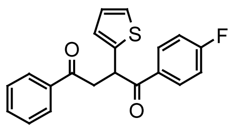
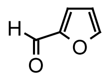
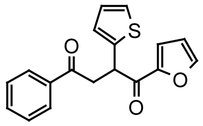
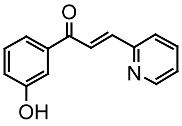
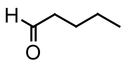
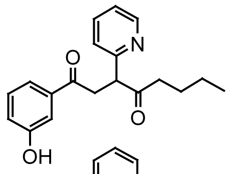
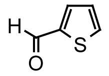
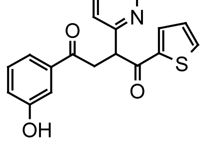
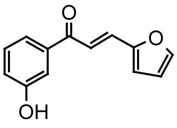
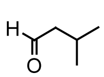
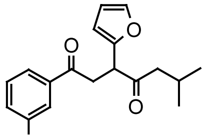
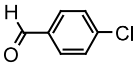
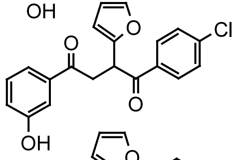
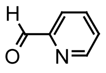
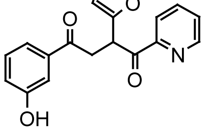
Table 1. Microwave-assisted synthesis of 1,4-dicarbonyl compounds

Entry	Enone **1**	Aldehyde **2**	1,4-Diketone[a] **3**	Microwave irradiation[b]		Conventional heating[c]	
				Time (min)	Yield(%)	Time (h)	Yield(%)
a				3.0	90	6.0	79
b	"			3.5	88	8.5	75
c	"			5.0	85	10.0	68
d				3.5	90	7.5	81
e	"			5.5	80	9.5	65
f	"			4.0	82	8.0	70
g				3.5	85	7.0	78
h	"			4.0	77	8.5	69
i				3.5	84	6.5	75
j	"			4.0	80	10.0	68
k	"			5.0	72	8.5	65

a: All products were characterized by ^{1}H, ^{13}C NMR, IR, and mass spectroscopy.
b: Pulsed irradiation (1 min with 20 sec intervals)
c: Refluxed in 1,4-dioxane

The reaction proceeded efficiently under microwave irradiation and solvent-free conditions. The reactions were carried out both under microwave as well as thermal conditions. Microwave irradiations were carried out using a BPL, BMO-800T domestic microwave oven operated at 2450 MHz (450 W). The reaction temperature was controlled using a pulsed irradiation technique (1 min with 20 s intervals). The temperature was measured after each pulse. The lowest observed temperature was 80°C after irradiation for one-minute at 450 W and the highest temperature was 110°C after 3 min irradiation at the same power. The reaction rates and yields were dramatically enhanced by microwave irradiation. The rate enhancement under microwave irradiation may be attributed to the absorption of more microwave energy by the polar media, which generates sufficient heat energy to promote the reaction. The same reaction, under thermal conditions, at 110°C took 6–10 h to afford yields comparable with those obtained by microwave irradiation. All the products were characterized by ^{1}H, ^{13}C NMR, IR, and mass spectroscopic data. Aliphatic aldehydes afforded excellent yields of products comparable to aromatic analogues. However, in the case of aromatic aldehydes, 5-(2-hydroxyethyl)-1,3-thiazolium bromide was used to promote the reaction as it was found to be more effective than the corresponding chloride. The scope and generality of this process is illustrated with respect to various aldehydes including aliphatic, aromatic, and heterocyclic ones as well as α,β-unsaturated ketones; the results are presented in Table 1.[8] In the absence of the base, the reactions of aromatic aldehydes proceeded only to a minor extent (15–25%) when the reactants were subjected to microwave irradiation under the influence of the thiozolium salt and basic alumina. In contrast, aliphatic aldehydes reacted smoothly with enones even in the absence of base under similar reaction conditions. Among various bases such as Et$_3$N, DBU, DABCO, and DBN studied for this reaction, DBU was found to be more efficient in promoting these reactions.

In summary, we have developed a simple, convenient and rapid method for the synthesis of 1,4-diketones from aldehydes and α,β-unsaturated ketones using a solid supported reagent system, i.e. thiazolium salt–DBU–Al$_2$O$_3$ under microwave irradiation. The present method avoids the use of solvent and extended reaction times and is a very useful preparation of γ-diketones especially from aromatic aldehydes, which typically give low yields of adducts under conventional conditions. The reduced reaction times together with the minimization of thermal decomposition of the products are the main advantages of microwave heating and further improvement would be facilitated by the availability of a continuous microwave reactor.

Acknowledgements

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8. *Typical procedure*: *n*-Heptanal (3 equiv.), 1,3-diphenyl-(*E*)-2-propen-1-one (1 equiv.), thiazolium salt (40 mol%) and DBU (1.5 equiv.) were admixed with basic Al$_2$O$_3$ (1.0 g) and the resulting solid was subjected to microwave irradiation using a BPL, BMO-800T domestic oven operated at 450 W for an appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was filtered and washed with dichloromethane (2×15 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na$_2$SO$_4$. Removal of the solvent under reduced pressure followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane 1:9) afforded the corresponding 1,4-diketone pure. Spectral data for selected compounds: 3a: ^{1}H NMR (CDCl$_3$, 200 MHz): δ 1.84 (s, 3H), 2.12 (s, 3H), 3.02 (dd, 1H, *J*=18.0, 3.9 Hz), 4.01 (dd, 1H, *J*=18.0, 9.9 Hz), 4.37 (dd, 1H, *J*=9.9, 3.9 Hz), 6.07 (s, 1H), 7.21–7.53 (m, 8H), 7.96 (d, 2H, *J*=7.8 Hz). ^{13}C NMR (CDCl$_3$): δ 20.8, 27.6, 42.0, 54.0, 123.5, 127.1, 128.0, 128.3, 128.8, 129.6, 132.8, 136.6, 138.8, 156.3, 197.9, 198.0. EIMS: *m*/*z* (%): 292 (M$^+$ 10), 210 (15), 141 (20), 105 (85), 83 (100), 77 (70). HRMS calcd for C$_{20}$H$_{20}$O$_2$: 292.1463. Found: 292.1498.
   3e: ^{1}H NMR (CDCl$_3$, 200 MHz): δ 3.37 (dd, 1H, *J*=18.5, 3.7 Hz), 4.21 (dd, 1H, *J*=18.5, 10.3 Hz), 5.50 (dd, 1H, *J*=10.4, 3.7 Hz), 6.88–7.62 (m, 8H), 7.94 (d, 2H, *J*=8.9 Hz), 8.10 (d, 2H, *J*=9.0 Hz). ^{13}C NMR (CDCl$_3$): δ 43.0, 44.2, 115.8, 125.2, 126.0, 127.3, 128.1, 128.6, 131.5, 132.5, 133.3, 136.1, 140.3, 167.3, 196.1, 197.5. EIMS: *m*/*z*: 338 (M$^+$ 35), 123 (100), 95 (40), 77 (25). HRMS calcd for C$_{20}$H$_{15}$O$_2$SF: 338.0776. Found: 338.0729.
   3g: ^{1}H NMR (CDCl$_3$, 200 MHz) δ: 0.90 (t, 3H, *J*=6.8 Hz), Hz), 1.13–1.28 (m, 2H), 1.40–1.58 (m, 2H), 2.32–2.65

(m, 2H), 3.22 (dd, 1H, $J=18.2$, 5.3 Hz), 3.94 (dd, 1H, $J=18.2$, 9.0 Hz), 4.58 (dd, 1H, $J=9.0$, 5.3 Hz) 6.90 (d, 1H, $J=9.0$ Hz), 7.08–7.41 (m, 5H), 7.63 (t, 1H, $J=7.8$ Hz), 8.55 (d, 1H, $J=5.3$ Hz). ^{13}C NMR ($CDCl_3$) δ: 13.4, 21.8, 25.4, 40.6, 41.5, 55.2, 114.7, 119.5, 120.7, 122.4, 123.3, 129.3, 137.3, 137.4, 149.1, 156.9, 157.5, 198.0, 208.4. EIMS: *m*/*z*: 311 (M^+ 90), 226 (5), 190 (8), 121 (15), 106 (40), 81 (60), 55 (100). HRMS calcd for $C_{19}H_{21}O_3N$: 311.1521. Found: 311.1561.