A Novel Approach to Synthesis of α,β-Unsaturated Ketones

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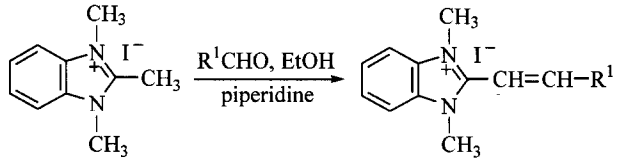
A new approach to the synthesis of α, β-unsaturated ketones from 1,2,3-trimethyl benzimidazolium salt via the condensation reaction with aldehydes followed by the addition reaction of Grignard reagents with quaternary C = N bond was provided.

Keywords α,β-unsaturated ketones, 1,2,3-trimethyl benzimidazolium salt, Grignard reagents, synthesis

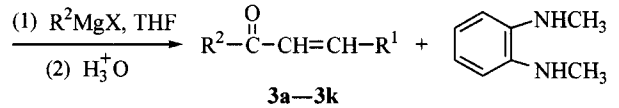
α,β-Unsaturated ketones are an important functional group in organic synthesis and have been widely used in the syntheses of many important pharmaceuticals and some compounds with particular structure.[1,2] An efficient preparation of α,β-unsaturated ketones has long been of interest and a series of new approaches has been reported.[3] In earlier paper,[4] the reaction of benzimidazole methiodide salts with Grinard reagents has been reported. In this paper, a convenient preparation of α,β-unsaturated ketones from 1, 2, 3-trimethyl benzimidazolium salt **1**, based on nucleophilicity of its 2-methyl carbon and electrophilicity of 2-carbon of 1,3-dimethyl-2-substituted ethenyl benzimidazolium salt **2**, via reaction in turn with aldehydesn[5] and Grignard reagents (Scheme 1) was described. Eleven α,β-unsaturated ketones (**3a—3k**) have been prepared.

1,3-Dimethyl-2-substituted ethenyl benzimidazolium iodides (**2a—2e**), which were easily obtained from the reaction of 1,2,3-trimethyl benzimidazolium iodide (**1**) with aldehydes, were reacted with Grignard reagents and then hydrolyzed with diluted HCl solution to produce the α,β-unsaturated ketones (**3a—3k**). The major advantages are the readily availability of the substrates, simplicity of isolation of the products and mild reaction conditions. The byproduct *N*,*N*′-dimethyl-1,2-benzenediamine can be reused.

Scheme 1



1 **2a—2e**



3a—3k

R^1: **2a**: C_6H_5; **2b**: *p*-$CH_3OC_6H_4$; **2c**: $(CH_3)_2CH$
2d: $CH_3(CH_2)_2$; **2e**: $CH_3(CH_2)_4$
R^1, R^2: **3a**: C_6H_5, CH_3; **3b**: C_6H_5, CH_3CH_2; **3c**: C_6H_5, C_6H_5
3d: *p*-$CH_3OC_6H_4$, CH_3; **3e**: *p*-$CH_3OC_6H_4$, CH_3CH_2
3f: *p*-$CH_3OC_6H_4$, C_6H_5; **3g**: $(CH_3)_2CH$, CH_3
3h: $CH_3(CH_2)_2$, CH_3; **3i**: $CH_3(CH_2)_2$, CH_3CH_2
3j: $CH_3(CH_2)_2$, C_6H_5; **3k**: $CH_3(CH_2)_4$, CH_3

The possible reaction mechanism (shown in Scheme 2) involves the addition of Grignard reagent to C = N bond of 1,3-dimethyl-2-substituted ethenyl benzimidazolium iodides followed by protonizing, opening the ring and hydrolyzing to give α,β-unsaturated ketones.

Experimental

Melting points were taken on a XT-4 micro-melting apparatus and uncorrected. Elemental analyses were performed with a PE-2400 instrument. IR spectra in cm^{-1}

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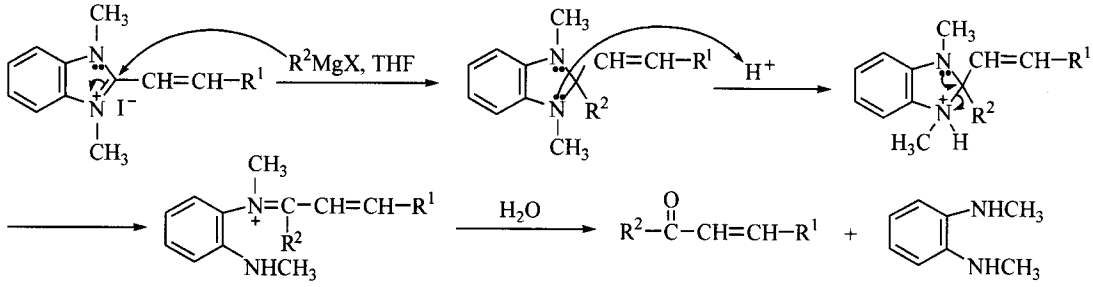
Scheme 2



were recorded on a Brucker EQUIOX-55 spectrometer. MS were taken on a HP5989B instrument. ^{1}H NMR spectra were recorded at 400 MHz on a Varian INOVA-400 spectrometer and chemical shifts were reported relative to internal Me_4Si. The UV absorption spectra were recorded on a General TU-1201 UV-vis spectrometer.

The reagents and solvents were available commercially. 1,2,3-Trimethyl benzimidazolium iodide (**1**) were prepared according to the literatures.[6]

Synthesis of **2a—2b**

A mixture of 1, 2, 3-trimethyl benzimidazolium iodide (10 mmol) (**1**) and aromatic aldehyde (10 mmol) was dissolved in 100 mL of anhydrous ethanol, then piperidine (3 mL) was added. The mixture was refluxed for 2 h and then cooled. The crude product was filtered and crystallized from alcohol-water to give pure compounds **2a—2b**.

2a Yellow solid (67%); m.p. 293—294 ℃; UV-vis (MeOH) λ_{max}: 322 (2.99×10^4) nm; ^{1}H NMR (D_2O) δ: 3.95 (s, 6H, NCH_3), 7.17 (d, J = 16.8 Hz, 1H, CH = CH), 7.40—7.42 (m, 3H, ArH), 7.51 (d, J = 18.0 Hz, 1H, CH = CH), 7.54—7.56 (m, 2H, ArH), 7.66—7.71 (m, 4H, ArH); IR (KBr) ν: 3024, 1624, 1514, 1476, 972, 763, 691 cm^{-1}; MS (70 eV) *m/z* (%): 233 (100), 234 (55), 218 (29), 142 (23), 127 (11), 116 (11), 77 (10); Anal. calcd for $C_{17}H_{17}N_2I$: C 54.29, H 4.52, N 7.45; found C 54.43, H 4.73, N 7.34.

2b Yellow solid (86%); m.p. 291—292 ℃; UV-vis (MeOH) λ_{max}: 348 (3.12×10^4) nm; ^{1}H NMR (DMSO-d_6) δ: 3.86 (s, 3H, OCH_3), 4.13 (s, 6H, NCH_3), 7.12 (d, J = 8.4 Hz, 2H, ArH), 7.42 (d, J = 16.0 Hz, 1H, CH = CH), 7.67—7.69 (m, 2H, ArH), 7.80 (d, J = 17.2 Hz, 1H, CH = CH), 7.92 (d, J = 8.4 Hz, 2H, ArH), 8.03—8.05 (m, 2H, ArH); IR (KBr) ν: 3022, 1633, 1518, 1474, 1250, 1022, 963, 818, 756 cm^{-1}; MS (70 eV) *m/z* (%): 263 (100), 220 (16), 142 (26), 127 (13), 77 (15), 15 (9); Anal. calcd for $C_{18}H_{19}N_2OI$: C 53.21, H 4.71, N 6.90; found C 53.05, H 4.75, N 6.93.

Synthesis of **2c—2e**

A mixture of 1, 2, 3-trimethyl benzimidazolium iodide (10 mmol) (**1**) and piperidine (3 mL) was dissolved in 100 mL of anhydrous ethanol and refluxed for 0.5 h. Aldehyde (10 mmol) was added dropwise to above solution. The mixture was refluxed for 2 h and then cooled. The solvent (60 mL) was removed and ether (10 mL) was added to above residue to give crude products. The crude products were chromatographed on a silica gel column eluting with methanol/acetic acid to give pure compounds **2c—2e**.

2c White solid (75%); m.p. 246—247 ℃; UV-vis (MeOH) λ_{max}: 280, 272, 220 nm; ^{1}H NMR (DMSO-d_6) δ: 1.39 (d, J = 6.0 Hz, 6H, CH_3), 4.01 (s, 6H, NCH_3), 6.76—6.80 (m, 1H, CH = CH), 7.13 (d, J = 16.0 Hz, 1H, CH = CH), 7.67—7.69 (m, 2H, ArH), 8.02—8.04 (m, 2H, ArH); IR (KBr) ν: 3025, 2963, 1618, 1522, 1478, 770 cm^{-1}; MS (70 eV) *m/z* (%): 215 (27), 201 (24), 199 (12), 173 (100), 171 (10), 146 (12), 142 (41), 131 (12), 127 (19), 77 (23), 43 (20), 15 (11); Anal. calcd for $C_{14}H_{19}N_2I$: C 49.16, H 5.56, N 8.19; found C 49.28, H 5.65, N 8.13.

2d White solid (73%); m.p. 198 ℃ (decom.); UV-vis (MeOH) λ_{max}: 280, 272, 216 nm; ^{1}H NMR (DMSO-d_6) δ: 0.85 (t, J = 12.0 Hz, 3H, CH_3), 1.43—1.47 (m, 2H, CH_2), 1.61—1.65 (m, 2H, CH_2), 4.07 (s, 6H, NCH_3), 6.80—6.84 (m,

1H, CH = CH), 6.98 (d, J = 16.4 Hz, 1H, CH = CH), 7.67—7.69 (m, 2H, ArH), 8.01—8.04 (m, 2H, ArH); IR (KBr) ν: 3022, 2962, 1617, 1533, 1479, 760 cm^{-1}; MS (70 eV) m/z (%): 214 (38), 199 (73), 185 (74), 171 (56), 146 (100), 142 (74), 131 (38), 127 (36), 77 (60), 43 (6), 15 (4); Anal. calcd for $C_{14}H_{19}N_2I$: C 49.16, H 5.56, N 8.19; found C 49.25, H 5.62, N 8.11.

2e White solid (76%); m.p. 205—207 ℃; UV-vis (MeOH) λ_{max}: 280, 272, 216 nm; ^1H NMR (DMSO-d_6) δ: 0.84 (t, J = 14.0 Hz, 3H, CH_3), 1.32—1.33 (m, 4H, $2CH_2$), 1.36—1.44 (m, 2H, CH_2), 1.62—1.65 (m, 2H, CH_2), 4.06 (s, 6H, NCH_3), 6.81 (d, J = 16.4 Hz, 1H, CH = CH), 6.96—7.00 (m, 1H, CH = CH), 7.67—7.69 (m, 2H, ArH), 8.01—8.04 (m, 2H, ArH); IR (KBr) ν: 3022, 2927, 1622, 1534, 1481, 760 cm^{-1}; MS (70 eV) m/z (%): 242 (29), 228 (14), 199 (100), 171 (27), 146 (47), 142 (32), 131 (20), 127 (23), 77 (27), 57 (4); Anal. calcd for $C_{16}H_{23}N_2I$: C 51.89, H 6.27, N 7.56; found C 52.01, H 6.30, N 7.49.

Synthesis of α,β-unsaturated ketones (**3a—3k**)

2-Substituted ethenyl-1,3-dimethyl benzimidazolium iodide (10 mmol) was added in small portions to a solution of Grignard reagent (30 mmol) in THF over 30 min. The mixture was stirred at room temperature for 18 h. A 10% solution of hydrochloride was added slowly (pH = 3—4) and the mixture was stirred for 45 min. THF was removed by distillation and the residue was extracted with ether or benzene (3 × 25 mL). The extract was washed with 5% sodium bicarbonate and dried over anhydrous magnesium sulfate. After removal of ether or benzene by distillation, the residue was distilled or crystallized. The results are given in Table 1.

Table 1 Experimental data of compound **3a—3k**

Compound	R^1	R^2	m.p. (℃)	b.p. (℃)	IR (C=O)(cm^{-1})	Yield (%)	m.p. (℃)[a]
3a	C_6H_5	CH_3	41 (42)[7]	–	1687	69	222—223 (221—222)[16]
3b	C_6H_5	CH_3CH_2	39—41 (38)[7]	–	1690	64	211—213 (211—212)[17]
3c	C_6H_5	C_6H_5	56—57 (58)[7]	–	1664	45	247—248 (248—249)[18]
3d	p-$CH_3OC_6H_4$	CH_3	71—73 (72—74)[8]	–	1680	72	225 (226, decom.)[8]
3e	p-$CH_3OC_6H_4$	CH_3CH_2	62 (61)[9]	–	1707	67	202—203 (200—201)[9]
3f	p-$CH_3OC_6H_4$	C_6H_5	75—76 (75)[10]	–	1650	50	–
3g	$(CH_3)_2CH$	CH_3	–	78—79/6.7 kPa (77.5/6.5 kPa)[11]	1709	70	171—172 (170.5)[11]
3h	$CH_3(CH_2)_2$	CH_3	–	63—64/2.0 kPa (64/2.9 kPa)[12]	1704	72	123—124 (124.5—125)[7]
3i	$CH_3(CH_2)2$	CH_3CH_2	–	85—86/4.8 kPa (83/4.6 kPa)[13]	1710	69	–
3j	$CH_3(CH_2)_2$	C_6H_5	–	80—82/0.020 kPa (78—79/0.013 kPa)[14]	1666	62	164—165 (162.5—163.5)[b,7]
3k	$CH_3(CH_2)_4$	CH_3	–	105—106/4.3 kPa (102—105/4.2 kPa)[15]	1702	75	84—85 (83—85)[19]

[a] m.p. of 2,4-dinitrophenylhydrazone. [b] m.p. of semicarbazone.

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