Microwave promoted novel synthesis of indenols catalyzed by SiO_2 in dry media

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Abstract
Indenols are produced in high yields when electron-rich α,β-unsaturated aldehydes adsorbed on silicon dioxide were subjected to microwave irradiation in dry media.

Keywords: Indenol, silicon dioxide, microwave, cyclization

Introduction

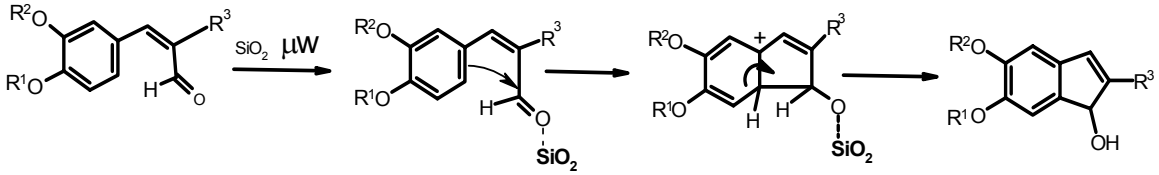
Indenols are an important class of compounds that exhibit broad spectrum of biological activity.[1] Despite their synthetic and pharmacological importance, few methods are known for the synthesis of these compounds and in majority of the cases transition metal catalyzed carbocyclization has been employed as the principal method for their preparation. Thus, Yamamoto *et al.* developed a novel palladium catalyzed (3+2) cycloaddition process[2a-c] to synthesize indenols, and ultimately indenones, using disubstituted alkynes as acceptor molecules. Vicente *et al.* described stoichiometric synthesis of indenols using mono or disubstituted alkynes and organomercurial compounds in the presence of palladium catalyst.[2d-f] Recently Cheng *et al*.[3a] reported an efficient route for disubstituted indenols through nickel catalyzed carbocyclization which was subsequently converted into an indenone derivative under base catalyzed oxidative cleavage conditions. Mayer *et al*.[3b] also reported a single example of the cyclization of the chloroformylation product (derived from propioveratrone) into the respective indenol under acid catalyzed conditions. As reported by Yamamoto *et al*. the ease of oxidation of indenols into synthetically and pharmacologically important indenones further increases the importance of synthetically accessing indenols. In the last few years 'Microwave-induced Organic Reaction Enhancement' (MORE) chemistry has gained popularity as a non-conventional technique for rapid, eco-friendly organic synthesis.[4]

The attractiveness of surface mediated dry reactions coupled with the microwave rate enhancement under non-solvent condition is also increased by the economic and environmental

advantages of this chemistry. Several high surface area solids such as clays, zeolites, SiO_2 and also alumina are employed for such purposes. Keeping in view the synthetic and biological importance of indenols, and our continued interest[5] in devising environmental friendly procedures for organic synthesis, we envisioned here a simple, rapid, eco-friendly, convenient, high yielding protocol for the generation of indenols from the electron rich α,β-unsaturated aldehydes under surface mediated 'dry media' conditions using microwave rate augmentation.

Results and Discussion

3, 4-Disubstituted aromatic ring with electron donating groups such as alkoxy α,β-unsaturated aldehydes adsorbed on silicon dioxide underwent cyclization when subjected to microwave irradiation under solvent free conditions to form indenols in high yields (85-92%). The irradiations were carried out in pulses so as to enable the monitoring of the reaction course by solvent extraction. The reaction is completely regio-selective and only a single regio-isomer was detected by ^{1}H-NMR in the crude product mixture. The presence of two singlets in the aromatic region of the ^{1}H-NMR (**4**) confirm the cyclization at sixth position of the aromatic ring, if cyclization occur at the second position, we would have got two doublets instead of two singlets. This is explained by the fact that the presence of electron donating group at the third position of the aromatic ring favors the formation of indenol, but there is no product formation in the absence of electron donating group at the third position. Even though, this reaction has limitation as far as the electron rich aromatic substitution is concerned, it is general with regard to the nature of group attached on the second constituent on the olefin.



Scheme 1. Microwave promoted synthesis of indenols.

Although the majority of reactions have been run in 0.5 mmol scale, when the reactions were up scaled to 5 mmol, identical yields were obtained as depicted in table. The reusability of SiO_2 has been established as results demonstrated that the catalyst could be recycled for three consecutive runs without apparent reduction in yields. The cyclization could also be affected by microwave irradiation of the compound adsorbed on Montmorillionite-K10 for 2-3 minutes at 800W however, this process afforded lower yields (30-40 %).

Table 1. Microwave promoted synthesis of indenols in dry media

Entry	Indenol [a]			Reaction Time	Yields [b] (%)
	R^1	R^2	R^3		
1	OMe	OMe	C_6H_5	12.0	88
2	OC_2H_5	OC_2H_5	C_6H_5	11.0	89
3	OC_2H_5	OC_2H_5	p-MeC_6H_4	10.0	92
4	OC_2H_5	OMe	C_6H_5	12.0	87
5	R^1, R^2= O-CH_2-O		C_2H_5	14.0	85
6	O-CH_2-O		C_6H_5	13.0	87
7	O-CH_2-O		C_9H_{19}	13.0	90

a) All products were characterized by IR, ^1H, ^{13}C and mass spectroscopy.
b) Yields obtained after column chromatography

In conclusion, we have demonstrated here a novel and solvent-free approach for the rapid and high yield synthesis of indenols using inexpensive silicon dioxide as a catalysts/solid support.

Experimental Section

General Procedures. Melting points were recorded on a Buchi Melting point apparatus D-545; IR spectra (KBr discs) were recorded on Bruker Vector 22 instrument. NMR spectra were recorded on a Bruker DPX 200 instrument in $CDCl_3$ with TMS as an internal standard for protons and solvent signals as internal standard for carbon spectra. Chemical shift values were mentioned in ppm. Mass spectra were recorded on EIMS (Shimadzu) instrument. Microwave irradiation was done by using domestic microwave oven (BPL –SANYO, 600 T). The progress of all reactions was monitored by TLC on 2x5 cm pre-coated silica gel 60 F254 plates of thickness of 0.25 mm (Merck). The chromatograms were visualized under UV 254-366 nm and iodine. Merck, 60-120 mesh Silica gel was used for column chromatography and surface media.
Experimental procedure. α,β-Unsaturated aldehyde (5 mmol) dissolved in dichloromethane (10ml), was admixed with silica gel (15.0 g), and the solvent was evaporated on rotary evaporator. The resulting fine powder was taken in a Pyrex test tube and subjected to microwave irradiation in domestic microwave oven, in pulses (800W, 2-3 minutes) for a total irradiation time ranging between 10-15 minutes. The reaction was monitored by TLC after each pulse. After complete conversion the mass was cooled to room temperature, extracted with dichloromethane (2x20 ml) and the combined organic extract was concentrated and the crude product was purified by silica gel chromatography elution gradients of hexane: ethyl acetate to afford pure indenols (**1-7**) in 85-92%.

Compound characterization. 5,6-Dimethoxy-2-phenyl-1*H*-inden-1-ol (1). M.p. 163 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.85 (s, 3H), 3.88 (s, 3H), 5.52 (s, 1H), 6.83 (s, 1H), 7.02 (s, 1H), 7.10 (s, 1H), 7.30 (m, 3H), 7.54 (d, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 56.21, 56.34, 58.11, 105.19, 108.50, 126.33, 127.76, 128.67, 133.21, 134.80, 136.74, 146.07, 148.36, 150.01; MS (EI, 70 eV): *m/z* : 252 (100%, M^+-16), 237 (63), 209 (20), 194 (20), 165 (66), 131 (23), 115 (29); IR (KBr, cm^{-1}): 692, 781, 1103, 1220, 1316, 1492, 1603, 2922, 3425. Elemental analysis calcd. for $C_{17}H_{16}O_3$, C = 76.10%, H = 6.01%. Found C = 76.21%, H = 5.90%.

5,6-Diethoxy-2-phenyl-1*H*-inden-1-ol (2). M.p. 166 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43-1.50 (m, 6H), 4.07-4.20 (m, 4H), 5.57 (s, 1H), 6.89 (s, 1H), 7.06 (s, 1H), 7.16 (s, 1H), 7.25-7.61(m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.88, 14.91, 58.13, 64.95, 65.15, 107.46, 110.93, 126.32, 127.69, 127.87, 128.64, 133.30, 134.98, 136.90, 145.97, 148.12, 149.80; MS (EI, 70 eV): *m/z* : 280 (100%, M^+-16), 251 (65), 223 (22), 194 (21), 115 (31); IR (KBr, cm^{-1}): 693, 801, 933, 956, 1252, 1442, 1473, 1501. Elemental analysis calcd. for $C_{19}H_{20}O_3$, C = 77.00%, H = 6.80%. Found C = 76.88%, H = 6.94%.

5,6-Diethoxy-2-(4-methylphenyl)-1*H*-inden-1-ol (3). M.p. 118 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43-1.56 (m, 6H), 2.38 (s, 3H), 4.07-4.14 (m, 4H), 5.55 (s, 1H), 6.88 (s, 1H), 7.0 (s, 1H), 7.19-7.25 (m, 3H), 7.49 (d, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.88, 14.91, 21.26, 58.22, 64.90, 65.13, 107.29, 110.93, 126.25, 126.92, 129.36, 130.51, 135.18, 136.72, 137.61, 146.00, 147.89, 149.75; MS (EI, 70 eV): *m/z* : 294 (100%, M^+-16), 265 (68), 237 (28), 208 (27), 115 (34); IR (KBr, cm^{-1}): 819, 1033, 1100, 1213, 1333, 1496, 1602, 2922, 3442. Elemental analysis calcd. for $C_{20}H_{22}O_3$, C = 77.39%, H = 7.14%. Found C = 77.44 %, H = 7.08%.

6-Ethoxy-5-methoxy-2-phenyl-1*H*-inden-1-ol (4). M.p. 156 °C; ^{1}H NMR (200 MHz, $CDCl_3$). δ 1.42-1.52 (m, 3H), 3.90 (s, 3H), 4.12-4.25 (m, 2H), 5.56 (s, 1H), 6.88 (s, 1H), 7.06 (s, 1H), 7.15 (s, 1H), 7.24-7.44 (m, 3H), 7.58 (d, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.89, 56.43, 58.16, 64.92, 105.56, 108.92, 127.84, 128.59, 128.68, 133.29, 134.83, 136.78, 145.98, 146.05, 147.68, 149.35; MS (EI, 70 eV): *m/z* : 266 (100%, M^+-16), 237 (64), 209 (20), 194 (22), 115 (30); IR (KBr, cm^{-1}): 690, 810, 940, 956, 1248, 1445, 1470, 1503. Elemental analysis calcd. for $C_{18}H_{18}O_3$, C = 76.58%, H = 6.42%. Found C = 76.70%, H = 6.52%.

6-Ethyl-5*H*-indeno[5,6-*d*][1,3]dioxol-5-ol (5). M.p. 125°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.2 (t, 3H), 2.42 (qt, 2H), 4.82 (s, 1H), 5.93 (s, 2H), 6.21 (s, 1H), 6.65 (1H, s), 6.99 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.55, 21.23, 77.60, 100.96, 101.93, 105.54, 124.41, 136.84, 138.80, 145.42, 147.64, 153.71; MS (EI, 70 eV): *m/z*: 204 (47.31%, M^+), 189 (100), 175 (21.5) , 131 (20.4), 103 (24.7), 77 (23.65), 63 (22.58), 41 (22.58); IR (KBr, cm^{-1}): 691, 782, 1040, 1195, 1328, 1470, 1600, 3435. Elemental analysis calcd. for $C_{12}H_{12}O_3$, C = 70.57%, H = 5.92%. Found C = 70.71%, H = 5.81%.

6-Phenyl-5*H*-indeno[5,6-*d*][1,3]dioxol-5-ol (6). M.p. 168°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.50 (s, 1H), 5.97 (s, 2H), 6.80 (s, 1H), 7.05 (d, 2H), 7.23-7.43 (m, 3H), 7.57 (d, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 57.57, 101.43, 102.71, 106.20, 126.29, 127.55, 127.80, 128.65, 133.06, 136.08, 138.23, 146.28, 146.85, 148.41; MS (EI, 70 eV): *m/z* : 236 (100%, M^+-16), 206 (31), 178 (57), 89 (24), 76 (20); IR (KBr, cm^{-1}): 692, 782, 879, 1037, 1195, 1332, 1472, 1599, 3448. . Elemental analysis calcd. for $C_{16}H_{12}O_3$, C = 76.17%, H = 4.79%. Found C =76.24%, H = 4.88%.

6-Nonyl-5*H*-indeno[5,6-*d*][1,3]dioxol-5-ol (7). M.p. 52°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, 3H), 1.27-1.42 (m, 14H), 2.37-2.48 (m, 2H), 4.98 (s, 1H), 5.94 (s, 2H), 6.32 (s, 1H), 6.68 (s, 1H), 6.98 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): 14.12, 22.68, 28.23, 28.24, 29.32, 29.42, 29.47, 29.55, 31.89, 60.26, 101.19, 102.04, 106.09, 126.72, 136.80, 137.44, 145.81, 148.03, 149.74; MS (EI, 70eV): m/z: 286 (99%, M^{+}-16), 187 (27), 173 (100), 115 (66); IR (KBr, cm^{-1}): 709, 861, 943, 1040, 1337, 1477, 2919, 3443.Elemental analysis calcd. for $C_{19}H_{26}O_3$, C = 75.47%, H = 8.66%. Found C = 75.33%, H = 8.78%.

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