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Domino synthesis of indenols and alkyl-indene ethers under modified Vilsmeier conditions

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Abstract—Indenols are produced in high yields through domino reactions, when electron-rich *trans*-stilbenes and other *trans* aryl–alkyl olefins were subjected to Vilsmeier formylation in the presence of excess $POCl_3$ in a one-pot procedure. The method is even suitable for converting aryl–alkyl carbinols (precursors for olefins) directly into indenols. The corresponding indene ethers could be prepared in high yields directly when less reactive α,β-unsaturated aldehydes were subjected to cyclization in alcoholic HCl.

Indenols are an important class of compounds that exhibit a broad spectrum of biological activity.[1] They also serve as the precursors for synthetically and biologically active indenones.[2] Despite the synthetic and pharmacological importance of indenols, few methods are known for the synthesis of these compounds and in the majority of cases, transition metal catalyzed carbocyclization has been employed as the protocol for their generation. Thus, Yamamoto and co-workers developed a novel palladium catalyzed (3+2)-cycloaddition process[3a–c] to synthesize indenols, 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 a palladium catalyst.[3d–f] Cheng and Rayabarapu reported an efficient route to disubstituted indenols through nickel catalyzed carbocyclization of *ortho*-halophenyl ketones with propiolates.[2a] Recently, Matsuda et al. reported a rhodium catalyzed annulation of acylphenylboronic acids with alkynes as a method for the preparation of indenols.[2i] Witiak et al. have reported the generation of *N*,*N*-dimethylamino indene derivatives under Vilsmeier conditions[2b] which were subsequently converted into indenone derivatives under base catalyzed oxidative cleavage conditions. Furthermore, Mayer and Bodendorf[2c] also reported the possibility of cyclizing the chloroformylation product (derived from propioveratrone) into indenols under acid catalyzed conditions, but the study was limited to this substrate alone. Thus, our literature survey revealed no general method for cyclizing electron-rich cinnamaldeyde derivatives (generated during the Vilsmeier reaction) concomitantly, into indenols, which could represent a straightforward and simple route.

Considering the importance of indenols as biologically active entities together with their synthetic importance, we envisioned a convenient, high yielding and efficient protocol for the generation of indenols and indene ethers using electron-rich *trans*-stilbenes and other *trans*-aryl–alkyl olefins under Vilsmeier conditions. We report that the Vilsmeier–Haack formylation reaction of stilbenes with electron-donating substitution on the aromatic rings formed indenols in moderate to high yields (72–91%) when excess $POCl_3$ was employed. The reactions were conducted by stirring the olefins with $POCl_3$ (>5 equiv) and DMF, at room temperature.[4]

Stilbenes with 3,4-disubstituted aromatic rings containing electron-donating groups such as alkoxy, methylenedioxy or hydroxy readily underwent cyclization without isolation of a formyl intermediate as cyclization occurred concomitantly. This method is adaptable even when carbinols (precursors for olefins) were directly employed and the indenols were formed without any apparent loss of yields. The *Z*-isomeric aldehyde,

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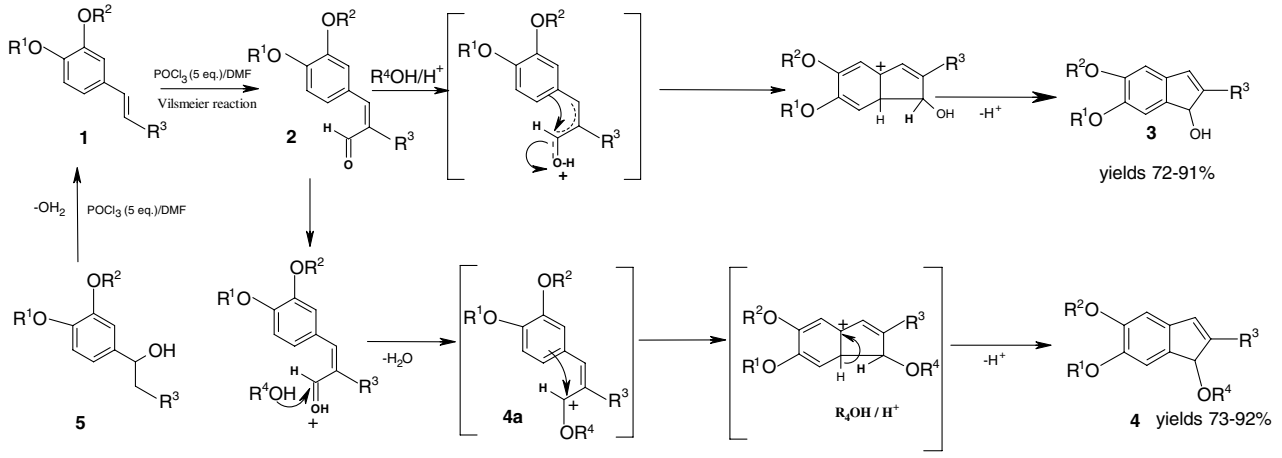
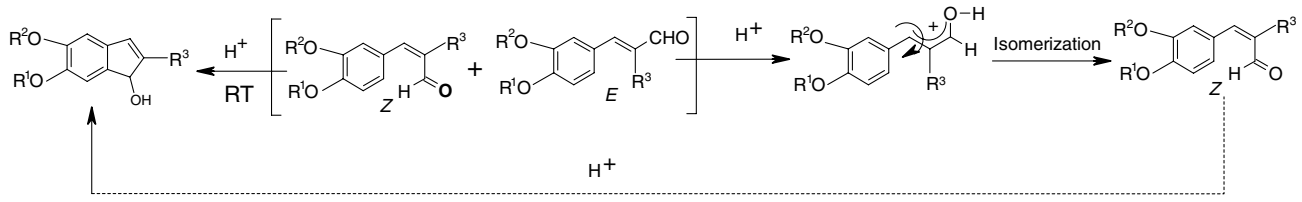


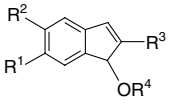
Scheme 1. Domino synthesis of indenols and alkyl-indene ethers under Vilsmeier conditions.



Scheme 2. Proton induced isomerization of substituted α,β-unsaturated aldehydes.

obtained as a minor product through Vilsmeier formylation at room temperature[2b] could also be converted into indenol. The unreacted predominant *E*-isomer could be readily cyclized by heating the reaction at 50 °C after quenching with water, a reaction which might be explained through proton induced *E*- to *Z*-isomerization of the α,β-unsaturated aldehyde as depicted in Scheme 2. Thus, excess $POCl_3$ not only helps in the dehydration of carbinols wherever employed as precursors, but also provides an acidic medium sufficient to affect cyclization of the formyl intermediates into indenols. However, when these reactions were conducted with an equimolar quantity of $POCl_3$ at room temperature, the corresponding formylated products were isolated whereas the reaction with an equimolar quantity of $POCl_3$ at >70 °C gave l-(*N*,*N*-dimethylamino)indene as the major product

Table 1. Preparation of indenol and alkyl indane ethers

Entry	 Indenol/alkyl-indene ether				Reaction time, h (conditions[b])	Yield[a] (%)
	R^1	R^2	R^3	R^4		
1	OMe	OMe	C_6H_5	H	45 (A)	84
2	OC_2H_5	OC_2H_5	C_6H_5	H	42 (A)	89
3	OMe	H	C_6H_5	CH_3	46 (C)	77
4	OC_2H_5	OC_2H_5	*p*-MeC_6H_4	H	40 (A)	91
5	OC_2H_5	OMe	C_6H_5	H	45 (A)	85
6	OC_2H_5	OMe	C_9H_{19}	H	50 (A)	82
7	OMe	OMe	C_2H_5	H	55 (A)	80
8	O–CH_2–O		C_6H_5	H	48 (A)	80
9	O–CH_2–O		$C_{11}H_{23}$	H	52 (A)	75
10	O–CH_2–O		C_9H_{19}	H	50 (A)	79
11	O–CH_2–O		C_2H_5	*i*-C_3H_7	12 (B)	73
12	O–CH_2–O		C_2H_5	*n*-C_4H_9	12 (B)	76
13	O–CH_2–O		C_2H_5	CH_3	12 (B)	92
14	O-CH_2–O		C_2H_5	H	58 (A)	72
15	O-CH_2–O		C_2H_5	H	3 min (D)	40

[a] Yields obtained after chromatographic purification.

[b] Reagents and conditions: (A) DMF/$POCl_3$ at rt; (B) stirring with alcoholic HCl; (C) reflux with methanolic HCl; (D) Montmorillonite K-10/microwave irradiation for 2 min at 800 W.

as explained by Witiak et al.[2b] In the case of 4-methoxy-substituted stilbenes, no cyclization was observed at rt (the corresponding formylated product was isolated in high yield) and required a higher temperature for cyclization to indenols. In the case of aryl–alkyl olefins, prolonged reaction followed by heating at 50 °C after quenching with water for 30–45 min resulted in complete cyclization of the intermediate aldehyde into indenols. Even though this reaction has some limitations with regard to the electron-rich substitution on the aromatic ring, it is general with regard to the nature of the alkyl group in the case of aryl–alkyl olefins.

The intermediate formylated products (α,β-unsaturated aldehydes) could also be readily cyclized to indenols after isolation, merely by heating with dilute aqueous HCl. Furthermore, this method offers a domino strategy for the generation of indene ethers if the reactions are conducted in the presence of alcoholic HCl. Indenol ethers[5] derived from various alcohols could be prepared by changing the alcohol component and the conversion was found to be general with regard to both primary and secondary alcohols. The formation of indene ethers on treatment of formylated olefins with alcoholic HCl might proceed through the generation of a relatively stable carbocation **4a** (Scheme 1) prior to cyclization and this was confirmed by the fact that indenols on treatment with alcoholic HCl failed to form the corresponding ethers even after prolonged reaction time, thus ruling out the possibility of ether formation via trapping of an indene carbocation. Although the majority of reactions were conducted on 0.5 mmol scale, when the reactions were up scaled to 5 mmol, identical yields were obtained. The cyclization could also be affected by microwave irradiation of the compound adsorbed on Montmorillonite-K10 for 2–3 min at 800 W, however, this process gave low yields (30–40%) (Table 1).

In conclusion, the present study reveals an easy access to substituted indenols and indene ethers, either from carbinols or the corresponding olefins. The synthetic protocol described in this paper is simple and convenient, involves the use of inexpensive reagents and provides a one-pot preparative procedure for these compounds.

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4. *Preparation of 5,6-dimethoxy-2-phenyl-1H-inden-1-ol. Typical procedure*: $POCl_3$ (3.84 g, 25 mmol) was added dropwise under an inert atmosphere to an ice-cold solution of 1,2-dimethoxy-4-[(*E*)-2-phenylvinyl]benzene (1.2 g, 5 mmol) in DMF (12 ml) over a period of 30 min and the resulting mixture was stirred at room temperature for 45 h. The reaction mixture was poured into ice-cold water and the resulting warm aqueous solution was stirred at 50 °C for 30 min, then cooled to rt and extracted with ether (3 × 20 ml). The combined ether extracts were washed with brine (20 ml) and dried (anhydrous Na_2SO_4). Evaporation of the solvent followed by flash chromatography ($SiO_2 > 200$ mesh, EtOAc/*n*-hexane gradient) gave 5,6-dimethoxy-2-phenyl-1*H*-inden-1-ol as a pale yellow solid (1.123 g, 84%). Mp 163 °C; IR (KBr, cm^{-1}): λ_{max} 692, 781, 103, 1220, 1316, 1492, 1603, 2922, 3425; ^1H NMR (200 MHz, $CDCl_3$): δ 1.51 (br s, 1H), 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, $J = 8.2$); ^{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). Elemental analysis calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.21; H, 5.90.
5. *Preparation of 6-ethyl-5-methoxy-5H-indeno[5,6-d][1,3]dioxole. Typical procedure*: (2*Z*)-2-(1,3-benzodioxol-5-ylmethylene)butanal (1.02 g 5 mmol) was stirred in the presence of a saturated solution of methanolic HCl (10 ml) at rt for 8 h followed by evaporation and aqueous work-up/solvent extraction to afford pure 6-ethyl-5-methoxy-5*H*-indeno[5,6-*d*][1,3]dioxole as a pale yellow solid (1.00 g, 92%). Mp 79.4 °C; IR (KBr, cm^{-1}): λ_{max} 860, 933, 1041, 1071, 1154, 1246, 1323, 1475, 1627, 2961, 3262; ^1H NMR (200 MHz, $CDCl_3$): δ 1.20 (t, 3H, $J = 7.4$), 2.31 (q, 2H, $J = 7.1$), 2.99 (s, 3H), 4.83 (s, 1H) 5.93 (s, 2H), 6.32 (s, 1H), 6.67 (s, 1H), 6.95 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.54, 20.54, 50.54, 82.33, 99.92, 100.92, 104.76, 125.10, 134.36, 136.73, 144.43, 146.64, 150.17; MS (EI, 70 eV): *m/z* 218 (55%), 203 (100), 189 (23), 174 (21), 145 (13), 128 (13), 115 (15), 102 (7), 77 (8), 63 (11), 52 (11). Elemental analysis calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.46; H, 6.53.