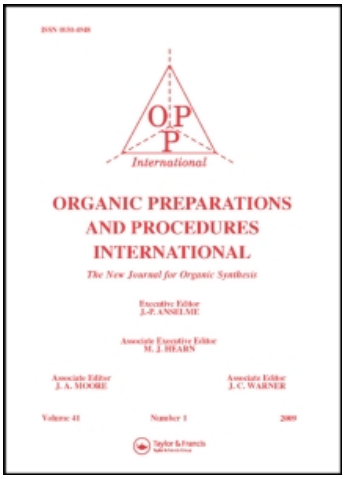

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Fei Liu[a]; Qi-Dong You[a]; Min-Yong Li[a]; Wen-Bin Shen[b]; Lin Xia[a]
[a] Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing, P R China [b] The Center for Instrumental Analysis, China Pharmaceutical University, Nanjing, P R China

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CONVENIENT AND RAPID PREPARATION OF INDENE DIMERS FROM INDENES OR INDANOLS

Submitted by (05/19/06)

Fei Liu[†], Qi-Dong You*[,†], Min-Yong Li[†], Wen-Bin Shen[††], and Lin Xia[†]

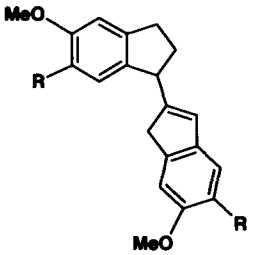
[†]*Department of Medicinal Chemistry, China Pharmaceutical University P. O. BOX 51, 24 Tongjiaxiang, Nanjing 210009, P. R. CHINA*

[††]*The Center for Instrumental Analysis, China Pharmaceutical University Nanjing 210009, P. R. CHINA*

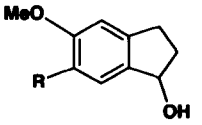
E-mail: youqd@cpu.edu.cn

Functionalized indenes and indans have been the subject of attention from medicinal and industrial chemists. 1-Aminoindanes are effective dopamine re-uptake blockers,[1] active against neurological disorders and neurotrauma[2] and, as their sulfonylated derivatives, are potential potassium channel blockers.[3] 3-(ω-Phthalimidoalkyl)indenes undergo intramolecular cyclization to form 13-membered spirocyclic nitrogen heterocycles upon irradiation and are useful intermediates in the synthesis of biologically active polycyclic compounds.[4] Naphthylidene-substituted aminoalkylindenes have high affinity toward and average pharmacological potency values at the cannabinoid receptor CB1.[5] Since indenes bearing an aromatic ring as substituted group display broad bioactivities, it was thought that indene dimers might desire further research for their bioactivities.

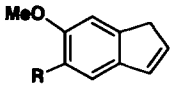
Classically, indene dimers have been prepared by treatment of indene or its derivatives, such as indanol, with mineral acids or Lewis acids. However, the dimerization of indene or indanol under acidic conditions is inconvenient leading to mixtures of several products.[6-8] Theoretically, 19 isomers could be obtained by the coupling of two indene molecules.[9,10] It was reported that treatment of 5,6-dimethoxy-1-indanol (**2b**) with 4 M HCl produced a mixture of **3b** and dimers **1b** and **4-6**.[6] Treatment of **2b** with triphenylphosphine in carbon tetrachloride-pyridine gave a mixture of **3b** and dimer **1b**.[6] Only when 5,6-dimethoxyindene (**3b**) was treated with silica and silver nitrate, was pure product **1b** obtained.[6] Other papers[7,8] describe the preparation of dimer **1b** by dehydration of indanol **2b** with thionyl chloride or oxalyl chloride. This paper reports convenient and rapid dimerization methods for indanol **2** or indene **3** in the presence of *p*-toluenesulfonic acid or HCl.



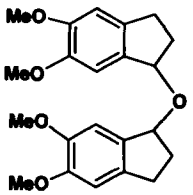
1a, R = H
1b, R = OMe



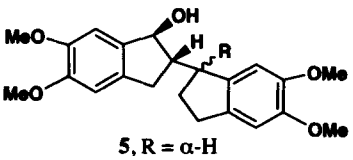
2a, R = H
2b, R = OMe



3a, R = H
3b, R = OMe



4

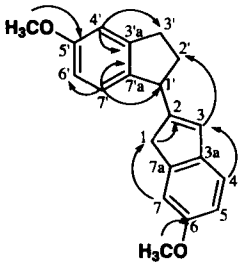


5, R = α-H
6, R = β-H

It was found that when 6-methoxyindene (**3a**) and 5,6-dimethoxyindene (**3b**) were stirred with conc. hydrochloric acid in benzene only for 10 min, pure dimers **1a** and **1b**, respectively, were obtained. No chlorinated products, such as 1-chloro-5-methoxy- 2,3-dihydroindene or 1-chloro-5,6-dimethoxy- 2,3-dihydroindene, were detected. This result was perhaps due to the two phase reaction conditions of benzene and hydrochloric acid. Based on this result, indanol was treated under the same conditions. However, a mixture was obtained, a fact which suggests that the two-phase conditions were not suitable for indanol. We changed the reaction conditions by using traces amounts of *p*-toluenesulfonic acid in toluene for 30 min and obtain pure **1a** and **1b**, respectively, from 5-methoxy-1-indanol (**2a**) and 5,6-dimethoxyindanol (**2b**).

The structures of **1a** and **1b** were established and confirmed by their elemental analysis as well as their ^{1}H NMR and ^{13}C NMR spectra. To ensure the site where C-2 connects to another indene, we analyzed the 2D NMR of **1a** (*Fig.*). The HMBC results confirmed the C-1' (δ 46.53)

correlation with CH-7' (δ 7.02, 1 H, d) and not with CH-4' (δ 6.81, 1 H, d) (*Table*). The structure of **1a** was elucidated by ^{1}H NMR, which showed H-2' at δ 2.06 and δ 2.44, H-3' at δ 2.96, H-1' at δ 4.22 and the methoxy group at δ 3.79. Assignment of other ^{1}H and ^{13}C NMR data for **1a** was made with the aid of HMBC and HSQC spectra (*Table*). The ^{1}H NMR of **1b** was very similar to **1a**. H-1', H-2', H-3', H-1 resonate from δ 2.05 to δ 4.19, and the signals from δ 6.48 to δ 7.04 were the aromatic protons and H-3.



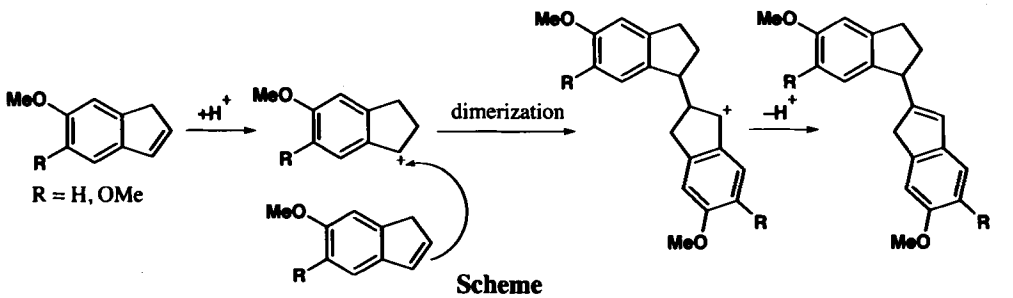
Major Correlations of HMBC Spectrum of 1a

Fig.

Table. NMR Data for Compound **1a** in $CDCl_3$

Position	^{13}C NMR	^{1}H NMR	DEPT
1	38.74	3.26 (m)	CH_2
2	150.59	----	C
3	126.36	6.50 (s)	CH
4	120.35	7.15 (d, J = 8.2)	CH
5	111.77	6.85 (m)	CH
6	157.39	----	C
7	110.57	6.95 (d, J = 1.8)	CH
1'	46.53	4.22 (t, J = 7.6)	CH
2'	34.14	2.06 (m) 2.4 (m)	CH_2
3'	31.95	2.96 (m)	CH_2
4'	109.93	6.81 (d, J = 2.3)	CH
5'	159.04	----	C
6'	112.26	6.78 (m)	CH
7'	125.18	7.02 (d, J = 8.2)	CH
3a, 7a	145.18, 145.44	----	C
3'a, 7'a	138.11, 138.40	----	C

The mechanism of the reaction may proceed *via* an indanyl carbocation generated from indene with hydrochloric acid which then couples with another indene to yield the dimerized carbocation intermediate, followed by loss of a proton (*Scheme*).



Scheme

EXPERIMENTAL SECTION

The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV 300 spectrometer using DMSO-d_6 or $CDCl_3$ as the solvent and TMS as the internal standard. Chemical shifts are reported in ppm units, and coupling constants (*J*) are in Hz. The EI-MS were obtained on SHIMADZU GCMS-QP2010. Elemental analyses were performed on a Carlo Erba 1106 instrument. Melting points (uncorrected) were obtained on a Thomas Hoover apparatus. The indenes **3a**, **3b** were synthesized according a literature precedure.[11]

Preparation of 6-Methoxy-2-(5-methoxy-2,3-dihydro-1*H*-inden-1-yl)-1*H*-indene (1a): *Procedure 1*.- To a solution of 0.15 g (1.03 mmol) of 6-methoxyindene (**3a**) in 10 mL of benzene was added 6 mL of conc. hydrochloric acid. After stirring at 50°C for 10 min, the solution was cooled to room temperature. The aqueous phase was separated and the organic phase was washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The light yellow oily residue was chromatographed (ethyl acetate/pet ether 1:9) on silica gel to give **1a** (0.11 g, 73%) as a white solid, mp 46-47°C; EI-MS (*m/z*) 292 (M^+); ^{1}H NMR and ^{13}C NMR: see *Table*.

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.16; H, 6.89. Found: C, 81.92; H, 6.77.

Procedure 2.- A solution of 1.0 g (6.09 mmol) of **2a** in 30 mL of dry toluene was heated under reflux for 30 min with 80.0 mg (0.75 mmol) of *p*-toluenesulfonic acid. The mixture was cooled, water was added, and the phases were separated. The aqueous phase was extracted with 30 mL of ether. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The light yellow oily residue was chromatographed as above to give **1a** (0.72 g, 81%).

Preparation of 2-(5,6-Dimethoxy-2,3-dihydro-1*H*-inden-1-yl)-5,6-dimethoxy-1*H*-indene (1b): *Procedure 1*.- 5,6-Dimethoxyindene (0.15 g, 0.85 mmol) (**3b**) was treated with hydrochloric acid as above to yield a white solid **1b** (0.12 g, 80%), mp 112-114°C, *lit.*[12] 113-114°C; EI-MS (*m/z*) 352 (M^+); ^{1}H NMR (DMSO-d_6): δ 2.05 (m, 1 H, H-2'), 2.37 (m, 1 H, H-2'), 2.86 (m, 2 H, H-3'), 3.21 (m, 2 H, H-1), 3.66 (s, 3 H, O-CH_3), 3.33 (s, 9 H, O-CH_3), 4.19 (t, 1 H, *J* = 7.4 Hz, H-1'), 6.48 (s, 1 H, Ar-H), 6.66 (s, 1 H, Ar-H), 6.88 (s, 1 H, Ar-H), 6.93 (s, 1 H, Ar-H), 7.04 (s, 1 H, Ar-H).

Anal. Calcd for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found: C, 74.83; H, 6.59.

Procedure 2.- A solution of 1.0 g (5.15 mmol) of **2b** and 70 mg (0.66 mmol) of *p*-toluenesulfonic acid in 30 mL of dry toluene was heated under reflux for 30 min. The mixture was then treated as above for **2a** to give **1b** (0.75 g, 83%).

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