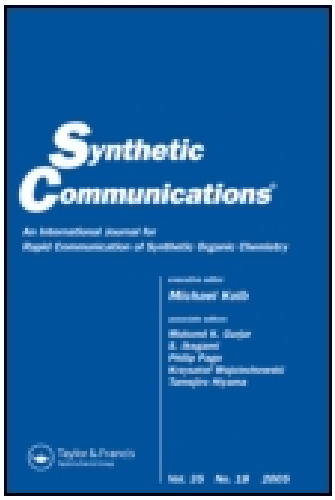

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A NEW AND EFFICIENT SYNTHESIS OF INDENONE

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A NEW AND EFFICIENT SYNTHESIS OF INDENONE

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ABSTRACT

Reaction of dichloroketone **2** with NEt_3 gave indenone (**4**) in high yield. Catodic reaction of **2** in the presence of C/Pt electrodes afforded the rearranged product **3** in high yield besides a small amount of chlorohydroxyketone **5**. Reaction of rearranged dichloroketone **3** with NEt_3 provided indenone (**4**) as the sole product. The mechanism of these reaction was discussed.

A rapid growth on the synthetic work of indenones took place in the last three decades. Indenones are useful intermediates[1] in the synthesis of a variety of molecules, including the C-nor D-homosteroid ring system,[2] photochromic indenone oxides,[3] 2,4- and 3,4-disubstituted-1-naphtols,[4] gibberellines,[5] indanones[6] and indenes.[7] A great deal of work has been directed

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towards the synthesis of the hindered fungicidally active 2-cyana-3-alkyl-1-indenones[8] and various 2,3-diaryl-1-indenones.[4,9–11] Furthermore, the derivatives of indanone exhibit biological activity[12] (e.g., antihypertensive or bronchodilatory activity) and they serve as synthetic precursors to other natural products (e.g., steroids or fermentation activators,[13] fungicides,[8] and potential estrogen binding receptors.[9]

Despite the considerable biological and synthetic interest in indenones, the development of general and flexible synthetic routes to these compounds still remains a challenging problem. Several procedures for the synthesis of indanones and indenols have been reported.[14] Mainly, two methods have been directed towards the synthesis of indenone derivatives. The first one[1,15] is palladium or aluminium chloride catalysed addition of substituted benzoil chlorides to acetylenic compounds. The variation of this reaction was achieved by Gevorgyan and Yamamato[14a,b] for the synthesis of indanones and indenols. The second method[13,16] involves an intramolecular Friedel-Crafts acylation of ß-chloro-ß-arylpropionyl chlorides followed by a dihydrochlorination reaction. The methodologies for the preparation of indenone are of rather limited use because of multistep, low yield, irreproducibility or decomposition of starting material. Several methods for the conversion of 1-indanone to indenone have been reported.[17] Marvel and Hinman[18] converted indanone to 2-acetoxy-1-indanone, and then from the pyrolyses of this compound they obtained indenone in 8.2% yield. They also obtained indenone from the bromination of indanone with NBS, followed by dehydrobromination of 3-bromoindanone. This synthesis was achieved by Minuti et al.[19] with a total of 65.8% yield. The similar methods have been reported by Bellamy[20] (78%) and Tidwell et al.[21] (24.7% yield except the last step). The bromination of 1-indanone with DBMA (5,5-dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane) gives 2-bromoindanone. The protection of carbonyl group followed by dehydrobromination, yields indenone ethylene ketal. The removal of the protecting group affords indenone. Floyd and Allen[16] synthesised indenone by the Friedel-Crafts acylation of ß-chloro-ß-arylpropionyl chlorides followed by a dehydrochlorination reaction in 44% yield. In this paper we report a new and efficient synthesis for the preparation of indenone (**4**).

The starting material **2**[22] was prepared by the addition of the dichloroketene to cycloheptatriene **1**. Reaction of dichloroketone **2** with NEt_3 (freshly distilled over metallic sodium) gave indenone as the sole product. The NMR spectral studies indicated that dichloroketone **3** was formed initially, which was then transferred into **4** (Scheme 1). This rearrangement is known as ''cine rearrangement'' with the reference to ''cine substitution'', a commonly used term for α' substitution of α-halocyclobutanones by external substituents.[23] The intermediate **3** was isolated by an independent reaction. Catodic reaction

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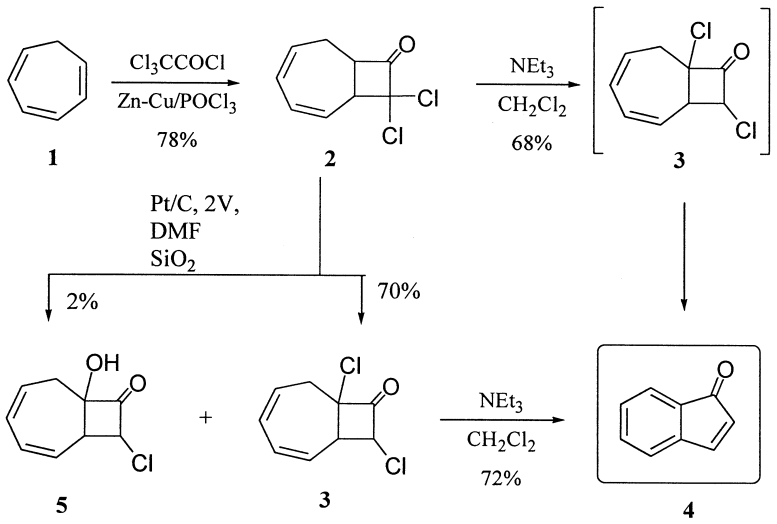


Scheme 1.

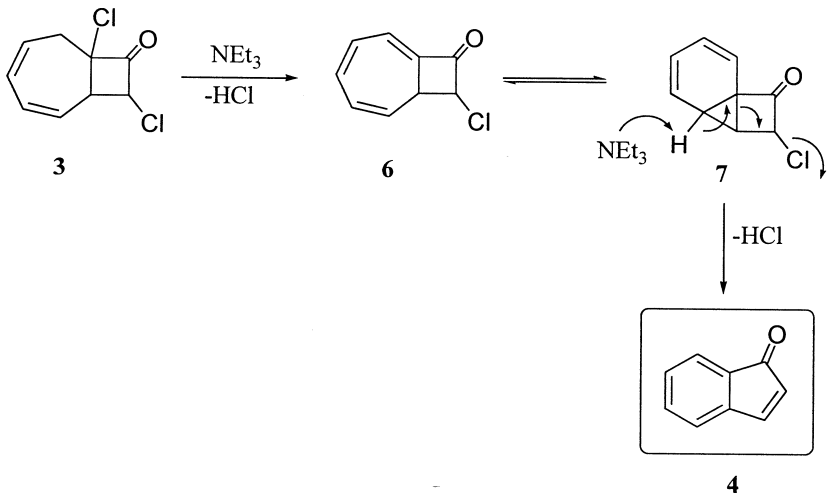
of **2** in the presence of C/Pt electrodes gave the rearranged product **3** in 70% yield besides a small amount of chlorohydroxyketone **5** which has probably been formed during the column chromatography. The structures of **3** and **5** have been elucidated on the basis of ^{1}H, and ^{13}C NMR data. Treatment of **3** with NEt_3 gave indenone as the sole product in 72% yield.

For this rearrangement we propose the following reaction mechanism. Firstly, the HCl elimination of **3** gives cycloheptatriene derivative **6** which will be in equilibrium with its valance isomer norcaradiene **7**. Further HCl elimination from **7** can result in the formation of indenone (Scheme 2).

In summary, we have developed an effective and simple synthetic methodology for the preparation of indenone (**4**). This methodology may also be applied to the synthesis of substituted indenones. Investigation of these types of reactions is currently under progress.

EXPERIMENTAL

General: Melting points are uncorrected. Infrared spectra were obtained from films on NaCl plates on a regular instrument. The ^{1}H and ^{13}C NMR spectra were recorded on 200- and 60-MHz spectrometers. Apparent splitting are given in all cases. TLC was carried out on Merck 0.2 mm silica gel 60 F254 analytical aluminium plates. Triethyl amine was freshly distilled over metallic sodium prior to use.



3 6 7 4

Scheme 2.

9,9-dichlorobicyclo[5.2.0]nona-2,4-dien-8-one (2)[22]: A 1L three-necked flask equipped with a condenser, addition funnel, and N_2 inlet was charged with 25 g (0.27 mol) of cycloheptatriene, 52.7 g of Zn-Cu (0.81 mol) and 300 mL of anhydrous diethyl ether. The suspension was stirred under N_2 and a solution of 58.9 g (0.324 mol) of trichloroacetylchloride and 49.7 g (0.324 mol) phosphoryltrichloride (distilled from potassium carbonate) in 100 mL of diethyl ether was added dropwise over 3 h. When the addition of the solution was complete, the mixture was refluxed with stirring for 24 hrs. The reaction mixture was then filtered through a pad celite and unreacted zinc was washed with 100 mL of diethyl ether. The etheral solution was washed with saturated $NaHCO_3$, water and dried with $MgSO_4$. The solvent was than removed in vacuo. The residue was filtered through a silica gel column (50 g) eluting with ethyl acetate/hexane (1:9) to give 44.0 g (0.216 mol, 78%) dichloroketone **2** as a pale yellow oil. **^{1}H NMR (200 MHz, $CDCl_3$)**: 5.7–6.3 (m, 4H, olefinic), 4.0 (ddd, $J = 11.3$, 8.7 and 5.2 Hz, 1H, H_7), 3.65 (dd, $J = 11.3$ and 3.4 Hz, 1H, H_1), 2.1–2.7 (m, 2H, H_6). **^{13}C NMR (50 MHz, $CDCl_3$)**: 197.84, 133.47, 131.03, 130.72, 130.67, 79.26, 68.05, 53.24, 29.75. **IR (neat, cm^{-1})**: 3055, 3010, 3000, 2927, 1829, 1472. $C_9H_8Cl_2O$ (203.1) calcd. C 53.23, H 3.97; found C 53.12, H 3.91.

The reaction of 9,9-dichloro-bicyclo[5.2.0^{1,7}]nona-3,5-diene-8-on (2) with NEt_3: To a magnetically stirred solution of dichloroketone **2** (4.0 g, 19.7 mmol) in 150 mL methylene chloride cooled to 10°C was added dropwise a solution of NEt_3 (freshly distilled over metallic sodium) (3.98 g, 39.4 mmol) in 10 mL methylene chloride during 15 min. This solution was

stirred for 2 h at 10°C. The solvent was removed approximately to 10% of original volume under reduced pressure at room temperature. To magnetically stirred residue was added ether (200 mL). The solution was filtered to remove the inorganic salts. The precipitated was washed with ether (3×50 mL). After removal of solvent, the residue was eluted over silica gel (10 g), with petroleum ether/ethyl ether (97:3) and indenone (**4**) was obtained as the sole product. **Indenon** (1.74 g, 68%), bright yellow oil: **^{1}H-NMR (200 MHz, $CDCl_3$)**: 7.56 (d, $J = 5.9$ Hz, A-part of AX system, 1H, H_3), 7.45–7.04 (m, 4H, aryl), 5.89 (d, B-part of AX system, $J = 5.9$ Hz, 1H, H_2). **^{13}C-NMR (50 MHz, $CDCl_3$)**: 200.17, 151.58, 146.65, 135.56, 132.44, 131.11, 129.21, 124.63, 124.15. **IR (NaCl, cm^{-1})**: 3029, 2927, 1753, 1727, 1625, 1548, 1472, 1370, 1293, 1191, 1038.

Catodic Reaction of 9,9-dichloro-bicyclo[5.2.0^{1,7}]nona-3,5-diene-9-on (2) in DMF: Into a 50 mL three-electrode H-cell fitted with Pt (anode) and graphite (cathode) electrodes were placed DMF (30 mL) and lithium perchlorate $LiClO_4$ (320 mg, 3 mmol) as electrolyte. Dichloroketone **2** (1.5 g, 7.39 mmol) was added to the cathode departure and after 12.7 Faradays/mol of electricity have been passed at a constant current of 15 mA (7 d, voltage: 2.1 V) through the solution, the solution was extracted with ether. The extract was washed with water and dried over $MgSO_4$. After removal of solvent, the residue was chromatographed over silica gel (100 g), with hexane/ethyl acetate (97:3) as the eluent. The first fraction identified as **7,9-dichlorobicyclo[5.2.0]nona-2,4-dien-8-one** (**3**): Pale yellow oil, 1.05 g, 70% yield. **^{1}H-NMR (200 MHz, $CDCl_3$)**: 6.33 (dd, $J = 11.2$ and 5.7 Hz, 1H, H_2), 6.22 (dd, $J = 10.5$ and 4.7 Hz, 1H, H_4), 6.15 (dd, 1H, $J = 11.2$ and 4.7 Hz, H_3), 5.95 (dt, $J = 10.5$ and 6.3 Hz, 1H, H_5), 4.79 (d, $J = 8.4$ Hz, 1H, H_9), 3.22 (dd, $J = 8.4$ and 5.7 Hz, 1H, H_1), 2.59 (d, $J = 6.3$ Hz, 2H, H_6) **^{13}C-NMR (50 MHz, $CDCl_3$)**: δ 199.11, 133.48, 132.50, 131.25, 130.50, 86.73, 66.61, 55.37, 36.47. **IR (NaCl, cm^{-1})**: 3055, 2978, 2902, 2851, 1829, 1446, 1268, 1217, 1063, 987, 844, 810.

Then the column was eluted with hexane/ethyl acetate (80:20). As the second we isolated hydroxy compound **9-chloro-7-dydroxybicyclo[5.2.0]-nona-2,4-dien-8-one: (5)** Pale yellow oil, 27 mg, 2%yield. **^{1}H-NMR (200 MHz, $CDCl_3$)**: 6.22–5.92 (m, 4H, H_2, H_3, H_4, and H_5), 4.98 (d, $J = 9.9$ Hz, 1H, H_9), 3.47 (bd, 1H, $J = 9.0$ Hz, H_1), 2.69 (dd, A-part of AB system, $J = 13.8$ and 5.0 Hz, 1H, H_{6a}), 2.4 (dd, $J = 13.8$ and 7.2, 1H, H_{6b}). **^{13}C-NMR (50 MHz, $CDCl_3$)**: δ 205.94, 132.43, 131.93, 131.22, 130.25, 102.54, 65.09, 50.16, 36.17. **IR (NaCl, cm^{-1})**: 3464, 3055, 2953, 1804, 1727, 1472, 1395, 1344, 1268, 1114, 1089, 936.

The reaction of 7,9-dichlorobicyclo[5.2.0]nona-2,4-dien-8-one (3) with NEt_3: To a magnetically stirred solution of dichloroketone **3** (2.0 g, 9.9 mmol) in 60 mL methylene chloride cooled to 10°C was added dropwise

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a solution of NEt_3 (freshly distilled over metallic sodium) (1.00 g, 9.9 mmol) in 5 mL methylene chloride during 15 min. This solution was stirred for 2 h at 10°C. The solvent was removed approximately to 10% of original volume under the reduced pressure at room temperature. To a magnetically stirred residue was added ether (150 ml). The solution was filtered to remove the inorganic salts. The precipitated was washed with ether (3×50 mL). After removal of solvent, the residue was eluted over silica gel (5 g), with petroleum ether/ethyl ether (97:3) and indenone (**4**) was obtained the sole product (0.92 g, 72% yield).

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