Indian Journal of Chemistry
Vol. 37B, October 1998, pp. 1027 - 1029

## Note

# An improved two-step regioselective synthesis of naphth[1,2,-*b*]- and naphth[2,1-*b*]oxepin-5-ones

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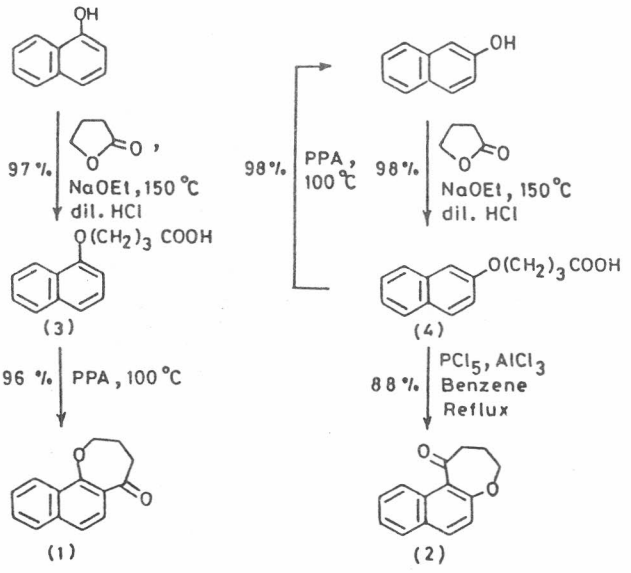
*Received 10 December 1996; accepted (revised) 25 September 1997*

An improved regioselective synthesis of naphth[1,2-*b*]oxepin-5-one **1** and naphth[2,1-*b*]oxepin-5-one **2** has been described. The key step is one-step regioselective synthesis of 4-naphthoxybutanoic acids **3** and **4**, formed from the corresponding naphthols, and their cyclisation to naphthoxepinones **1** and **2**.

Synthesis of annelated oxepins is of much interest as these compounds possess marked pharmacological effects[1-4]. The effect of aromatic ring annelation in relation to conformations of 1-benzoxepins has been studied by us in details[5-7].

In continuation of our work on the conformational studies of naphtho annelated oxepins, we required naphthoxepinones **1** and **2**. The only method available in literature for the synthesis of **3** and **4** and their cyclisation to **1** and **2** has been reported by Cagniant *et al.*[8]. Their method consists of a two-step synthesis of **3** and **4** from 1- and 2-naphthols respectively by first conversion of naphthols into naphthoxybutyrates and subsequent hydrolysis to the corresponding acids **3** and **4**. Their method involves more steps, longer reaction period and gives lower yield without mention of appropriate spectroscopic data compared to ours one-step method which afforded the acids **3** and **4** in 97% and 98% yields respectively. Our method for the synthesis of **3** and **4** consists of regioselective condensation of naphthols with γ-butyrolactone in NaOEt at 150°C, Cyclisation of **3** with PPA at 100°C gave **1** in 96% yield compared to 80% reported by Cagniant *et al.*[8]. However, the attempted cyclisation of **4** with PPA at 100°C led to exclusive formation of 2-naphthol in 98% yield. The formation of 2-naphthol was evidenced by comparison of HPLC with an authentic sample, $^1$H NMR and mass (EI) spectra. The formation of 2-naphthol is possibly due to facile rupture of C-O bond in β-isomer of the acid **4** at higher temperature which is not observed in α-isomer of the acid **3**. Similar cyclisation of **4** with PPA described by Cagniant *et al.*[8] has been reported to result in the formation of **2** alongwith regioisomer. The regioselective cyclisation of **4** in 88% yield was accomplished by first conversion of **4** into its acid chloride with $PCl_5$ and then cyclisation with anhydrous $AlCl_3$ in $CS_2$ (**Scheme I**). The regioisomer formed by cyclisation with $PCl_5$ and $AlCl_3$ was assigned the structure **2** by comparison with an authentic sample prepared according to method of Cagniant *et al.*[8]. In short, we have described a simple two-step efficient method for regioselective synthesis of naphth[1,2-*b*]- and naphth[2,1-*b*]oxepin-5-ones in much improved yield than the literature procedure.




**Scheme I**

**Stereochemical Assignments.** Like benzoxepins[6,7] both naphtho[1,2-*b*]- and naphtho[2,1-*b*]oxepins exist predominantly in boat and twist chair conformations as shown in **Figure 1** and **Figure 2**. The rate of inversion of boat to chair in

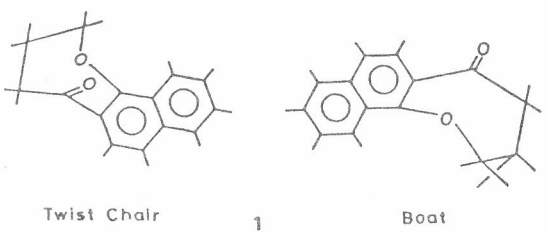



Figure 1

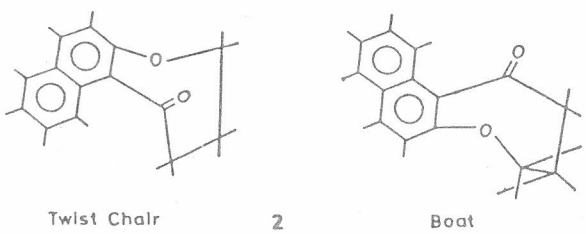



Figure 2

naphthoxepins compared to oxepins[9] is further reduced by naphthalene ring.

## Experimental Section

**General.** Melting points are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 137 spectrophotometer. $^1$H NMR spectra were recorded on a 90 MHz Perkin-Elmer R-32 instrument in δ-scale downfield from the internal $Me_4Si$. Mass spectra was recorded on a Jeol-JMS-300 MS-spectrometer. Various spectra were recorded and elemental analyses carried out by RSIC of Central Drug Research Institute, Lucknow.

**General procedure for synthesis of 4-naphthoxybutanoic acids.** 1- or2-Naphthol (1.44 g, 10 mmoles) was added to NaOEt (prepared from 0.25 g Na and 5 mL abs. EtOH). After 5 min γ-butyrolactone (0.86 g, 10 mmoles) was added and reaction mixture refluxed for 5 hr. The solvent (EtOH) was distilled off and residue heated at 150°C for 12 hr. The solid mass was cooled, diluted with $H_2O$ and acidified with dil HCl. The product thus separated was filtered and crystallized from EtOH to furnish the pure naphthoxybutanoic acid **3** or **4**.

**4-(1-Naphthoxy)butanoic acid 3:** Yield 2.23 g (97%), mp 120°C (lit.[8] 120°C); IR: 1695, 3450 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 1.6-2.6 (m, 4H, 2×$CH_2$), 3.82 (t, 2H, *J*=7 Hz, $OCH_2$), 6.3-8.1 (m, 8H, naphthyl protons and OH); MS: m/z 230 ($M^+$). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.04; H, 6.08. Found: C, 73.17; H, 6.0%.

**4-(2-Naphthoxy)butanoic acid 4:** Yield 2.25 g (98%), mp 128°C (lit.[8] 124°C); IR: 3450, 1700 cm$^{-1}$, $^1$H NMR ($CDCl_3$+DMSO-$d_6$): δ 1.8-2.7 (m, 2H, 2×$CH_2$), 4.03 (t, 2H, *J*=7 Hz, $OCH_2$), 6.5-8.2 (m, 7H, naphthyl protons), 9.56 (s, 1H, OH); MS: m/z 230 ($M^+$). Anal. Calcd $C_{14}H_{14}O_3$: C, 73.04; H, 6.08. Found: C, 73.23; H, 6.24%.

**2,3,4-5-Tetrahydronaphth[1,2-*b*]oxepin-5-one 1.** A mixture of 4-(1-naphthoxy)butanoic acid **3** (2.30 g, 10 moles) and PPA (46 g) was heated at 100°C for 2.5 hr. The red coloured syrup thus obtained was poured onto crushed ice, extracted with $CHCl_3$, washed with aq. $NaHCO_3$ (10%) and brine, dried ($Na_2SO_4$) and concentrated under reduced pressure to give the crude product which was further purified by crystallization from benzene-hexane to furnish **1** as colourless crystals, yield 2.50 g (96%), m.p. 112°C (lit.[8] 82°C); IR: 1700 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.0-2.9 (m, 4H, 2×$CH_2$), 4.21 (t, 2H, *J*=7 Hz, $OCH_2$), 6.7-8.5 (m, 6H, naphthyl protons); MS: m/z 212 ($M^+$). Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.24; H, 5.66. Found: C, 79.18; H, 5.58%.

**2, 3, 4, 5-Tetrahydronaphth[2,1-*b*]oxepin-5-one 2.** A solution of 4-(2-naphthoxy)butanoic acid **4** (2.30 g, 10 mmoles) in dry benzene (30 mL) and $PCl_5$ (3.12 g, 15 mmoles) was refluxed for 3 hr, and concentrated *in vacuo*. The acid chloride thus formed was dissolved in dry $CS_2$ (40 mL) and anhydrous $AlCl_3$ (10 g) added to the solution at 0°C, and the mixture refluxed for 4 hr. $CS_2$ was distilled off and the product poured onto ice cooled HCl, and extracted with $CHCl_3$ (4×30 mL). Chloroform layer was washed with brine, dried ($Na_2SO_4$) and concentrated *in vacuo* to give a light brown solid which was crystallised from benzene-hexane to yield **2** as colourless crystals, yield 1.87 g (88%), mp 138°C; IR: 1710 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.0-2.85 (m, 4H, 2×$CH_2$), 4.18 (t, 2H, *J*=7 Hz. $OCH_2$), 6.0-8.3 (m, 6H, naphthyl protons); MS: m/z 212 ($M^+$). Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.24; H, 5.66. Found: C, 79.20; H, 5.66%.

## Acknowledgement

Financial assistance from UGC, New Delhi is gratefully acknowledged.

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