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Short and Selective Synthesis of 3,5-dibromoinden-1-one

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Abstract

Brominations of hydrocarbons are important processes in synthetic chemistry. Bromoindanes and bromoindenones are key intermediate for medicinally valuable compounds. Short and efficient synthesis of 3,5-dibromoinden-1-one is presented. 5-bromoindane-1-one **1** was treated with ethylene glycol to mask the ketone functional group to yield the cyclic ketal **2**. Bromination of bromoindanecyclic ketal **2** with bromine in photochemical reaction apparatus while being irradiated with a projector lamp afforded the product which was treated with silica gel directly to remove the protective group afforded the corresponding 3,5-dibromoinden-1-one **3**.

Key words: *Photobromination, 5-bromoindanone ethylene ketal, 3,5-dibromoinden-1-one, protecting group, radical mechanism.*

1. Introduction

Brominations of hydrocarbons are important processes in synthetic chemistry [1-3]. They are precursors in the preparation of organometallic reagents [4] as well as the metal mediated coupling reactions [5-7].

Indanes have found widespread application as biologically important substructures in medicinal chemistry [8-11] as well as they exhibit the luminescent properties [12]. 5-bromoindane-1-one **1** is the starting compound for many pharmaceutically valuable products. Dinges *et al* [13] synthesised compounds, exhibiting kinase inhibitors and antitumor efficacy in human breast carcinoma from 5-bromoindane-1-one **1**. Due to the good leaving group of bromine, it was substituted with aldehyde, hydroxyl, *N*-methylpiperazine, 2-chloroethyl methyl ether yielded the bioactive compounds. Hark *et al* [14] have reported the bromination

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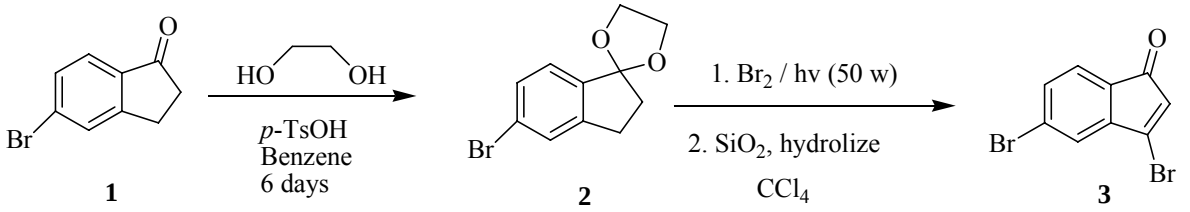
of 6-bromoindane-1-one wiht NBS and catalytic amount of AIBN in CCl_4 at reflux while being irradiated with a 150 W light to afford 3,6-dibromoinden-1-one but the yield was rather low (15%). Two bromine were bonded to our target molecule so it could be key intermediate for synthesising medicinally important compounds.
Herein we developed short and efficient route for synthesising 3,5-dibromoinden-1-one which wasn't reported before.

2. Results and Discussion

The treatment of 5-bromoindane-1-one **1** with ethylene glycol in benzene at reflux for 6 days in the presence of *p*-TsOH yielded the corresponding bromoindanecyclic ketal **2** [13] in a yield of 72%. The ^{1}H-NMR spectrum of cyclic ketal **2** confirmed the proposed structure. Aliphatic protons gave rise to an AA'BB' system. AA' part of the system resonated at δ 2.74 as a triplet and BB' part of the system gave the signal at δ 2.15 which belonged to benzylic protons. Ten lines in ^{13}C NMR spectra are also in agreement with the proposed structure. The reaction of cyclic ketal **2** with bromine in photochemical reaction apparatus while being irradiated with a 50 W projector lamp for 3 h afforded the product which was treated with silica gel for removing the protective group to yield the corresponding 3,5-dibromoinden-1-one **3** in 46% yield. If molecular bromine is used instead of photobromination without protecting of carbonyl group, the bromination will take place at α-position [15] therefore photobromination and protect the carbonyl are crucial to take place the bromination at β-position (Scheme 1).

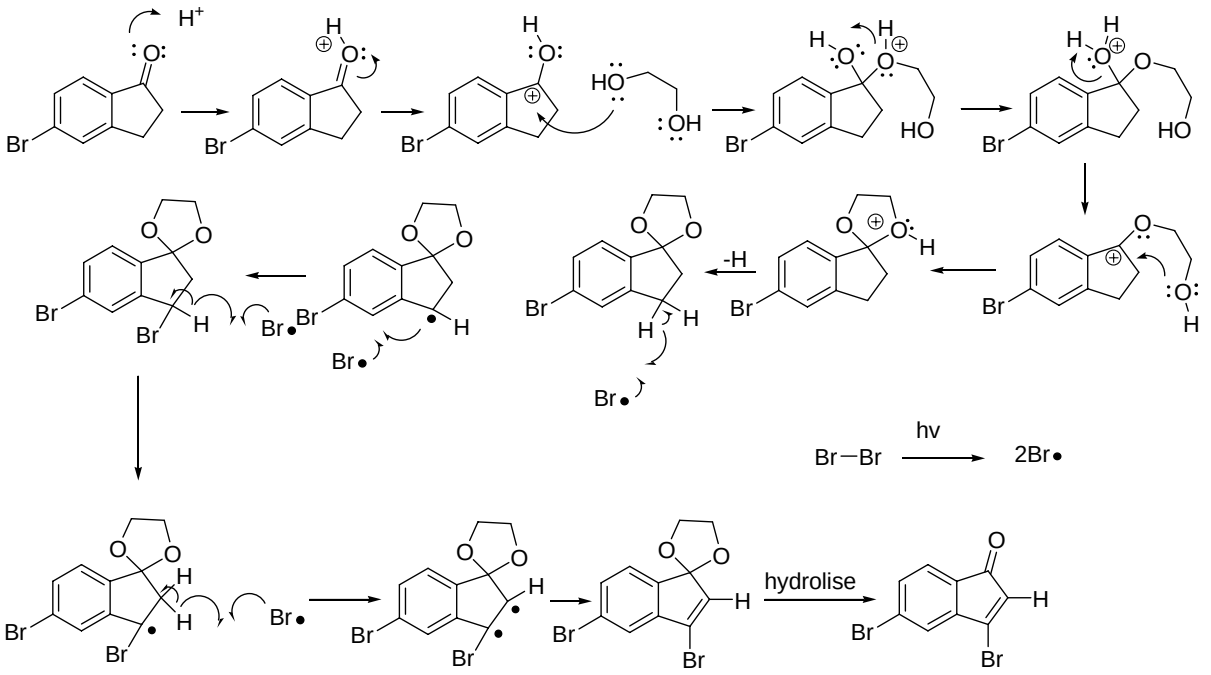


Scheme 1: Synthesis of 3,5-dibromoinden-1-one

In ^{1}H-NMR spectrum, three protons resonated at aromatic region therefore bromine bonded to aliphatic carbon. The aromatic protons shifted slightly downfield as compared to cyclic ketal due to the bromine bonded to C-3 caused the deshielding effect. The olefinic proton appeared deshielded at δ 6.2 as a singlet due to the electron withdrawn effects of the carbonyl group. In ^{13}C-NMR spectrum, observation of nine peaks is fully in agreement with the proposed structure. Carbonyl carbon signal appeared at δ 192.8 and all other carbon signals were observed at olefinic and aromatic regions indicated that presence of double bond at five membered ring moiety Reaction mechanism is shown in scheme 2.

3. Experimental

General Procedures: Column chromatography was carried out on Silica Gel 60 (230-400 mesh, E. Merck). TLC was performed on pre-coated glass plates of silica gel 60 F_{254} (0.25 mm, E. Merck). Melting points were determined with a Büchi B-540 apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded with 300 and 75 MHz Bruker instrument. Chemical shifts are in ppm from Me_4Si, generated from the $CDCl_3$. IR spectra were taken with a Perkin-Elmer Paragon 1000 FT-IR spectrometer.



Scheme 2: Reaction mechanism of 3,5-dibromoinden-1-one

3.1 Synthesis of 5-bromoindanone ethylene ketal 2

To a round bottom, two necked reaction flask, a solution of 5-bromoindane-1-one **1** (0.5 g, 2.4 mmol) in benzene (30 ml), ethylene glycol (1.25 g, 20 mmol) and catalytic amount of *p*-TsOH were added. Dean-Stark apparatus and a condenser were connected to the reaction flask. After the reaction mixture was refluxed for 6 days, it was extracted with 5% $NaHCO_3$ (3×20 ml), dried ($MgSO_4$), concentrated, yielded the 5-bromoindanone ethylene- ketal **2** (0.43 g, 72%) as a yellow solid. IR: υ/cm^{-1} (KBr): 3390, 2922, 1700, 1591, 1570, 1435, 1411, 1317, 1265, 1051. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23-7.07 (m, 3H, Ar), 3.96 (m, 4H**,** 2xOCH_2), 2.74 (t, 2H, J = 6.9 Hz, CH_2), 2.15(t, 2H, J = 6.9 Hz, CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 146.1, 141.5, 130.3, 128.5, 125.0, 123.8, 116.8, 66.4, 37.3, 28.6.

3.2 Synthesis of 3,5-dibromoinden-1-one 3

5-bromoindanketal **2** (0.5 g, 1.95 mmol) was dissolved in CCl_4 (30 ml) in photochemical reaction apparatus equipped with a reflux condenser. A solution of bromine (0,76 g, 4,3 mmol) in carbon tetrachloride (20 mL) was added dropwise to the solution over a time period of 1 h, while irradiating with a 50-W projector lamp. The resulting solution was stirred for an additional 2 h. HBr was rigorously removed during the reaction. After being cooled to room temperature, the excess bromine and solvent were removed under reduced pressure to yield the product which was treated with silica gel (10 g, 60, 70-230 mesh) for 24 h to afford the yellow solid, 3,5-dibromoinden-1-one **3** (0,3 g, %46). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7,42 (dd, J=7.5 Hz, J = 1.8 Hz, 1H), 7.29 (d, J = 1.8 Hz, 1H), 7.05 (d, J = 7.5 Hz, 1H), 6.20 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 192.8, 147.2, 144.9, 133.3, 129.2, 128.7, 128.6, 125.2, 123.3. IR: υ/cm^{-1} (KBr): 3091, 2848, 1700, 1591, 1535, 1446, 1334, 1253, 1178, 821. Anal. Calcd for $C_9H_4Br_2O$: C, 37.54, H, 1.40%. Found: C, 37.45, H, 1.34%.

References

[1] O. Cakmak, R. Erenler, A. Tutar and N. Celik, Synthesis of New Anthracene Derivatives, J. Org. Chem., 71 (2006) 1795-1801.

[2] R. Erenler, I. Demirtas, Bulent Buyukkidan, O. Cakmak, Synthesis of hydroxy, epoxy, nitrato and methoxy derivatives of tetralins and naphthalenes, J. Chem. Res., (2006) 753-757.

[3] R. Erenler, O. Cakmak, Synthesis of hexabromo, hydroxy, epoxy, methoxy and nitroxy derivatives of tetralins and naphthalenes, J. Chem. Res., (2004) 566-569.

[4] H. L**.** Anderson, C. J. Walter, A. Vidal-Ferran, R. A. Hay, P. A. Lowden, J. K. M. Sanders, Octatetrayne-linked porphyrins: 'stretched' cyclic dimers and trimers with very spacious cavities, J. Chem. Soc., Perkin Trans. 1**,** 18 (1995) 2275-2279.

[5] J. K. Still, Palladium-catalyzed coupling of organotin reagents with organic electrophiles. Pure Appl. Chem**.,** 57 (1985) 1771-1780.

[6] N. Miyaura, A. Suzuki, Palladium-catalyzed cross-coupling reactions of organoboron compounds, Chem. Rev., 95 (1995), 2457–2843.

[7] I. P. Beletskaya, A. V. Cheprakov, Heck reaction as a sharpening stone of palladium catalysis, Chem. Rev., 100 (2000) 3009–3066.

[8] H. Hu, S. P. Hollinshead, S. E. Hall, K. Kalter, L. M. Ballas, Synthesis and protein kinase C inhibitory activities of balanol analogues with modification of 4-hydroxybenzamido moiety, Bioorg. Med. Chem. Lett., 6 (1996**)** 973-978.

[9] S. Ulmschneider, U. Mulller-Vieira, C. D. Klein, I. Antes, T. Lengauer, R.W. Hartmann, Synthesis and evaluation of (pridylmethylene)tetrahydronaphthalenes / -indanes and structurally modified derivatives potent and selective inhibitors of aldosterone synthase, J. Med. Chem., 48 (2005) 1563-1575.

[10] M. F. Gross, S. Beaudoin, G. McNaughton-Smith, G. S. Amato, N. A. Castle, C. Huang, A. Zou, W. Yu*,* Aryl sulfonamido indane inhibitors of the Kv1.5 ion channel, Bioorg.Med. Chem. Lett. 17 (2007) 2849-2853.

[11] S. Hudson, M. Kiankarimi, W. Eccles, Y. S. Mostofi, M. J. Genicot, W. Dwight, B. A. Fleck, K. Gogas, W. S. Wade, Synthesis and structure–activity relationships of selective norepinephrine reuptake inhibitors (sNRI) with a heterocyclic ring constraint, Bioorg. Med. Chem. Lett., 18 (2008) 4495-4498.

[12] H. Wang, P. He, H. Yan, M. Gong, Synthesis, characteristics and luminescent properties of a new europium(III) organic complex applied in near UV LED, Sensors and Actuators B: Chemical, 156 (2011**)** 6-11.

[13] J. Dinges, D. H. Albert, L. D. Arnold, K. L. Ashworth, I. Akritopoulou-Zanze, P. F. Bousquet, J. J. Bouska, G. A. Cunha, S. K. Davidsen, G. J. Diaz, S. W. Djuric, A. F. Gasiecki,G. A. Gintant, V. J. Gracias, C. M. Harris, K. A. Houseman, C. W. Hutchins, E. F. Johnson,H. Li, P. A. Marcotte, R. L. Martin, M. R. Michaelides, M. Nyein, T. J. Sowin, Z. Su,P. H. Tapang, Z. Xia, and H. Q. Zhang, Alkynyl sub 1,4-dihydroindeno[1,2-c]pyrazole potent multitargeted receptor tyrosine kinase inhibitor with low hERG affinity, J. Med. Chem., 50 (2007) 2011-2029.

[14] R. R. Hark, D. B. Hauze, O. Petrovskaia, and M. M. Joullie, Synthetic studies of novel ninhydrin analogs, Can. J. Chem., 79 (2001) 1632–1654.

[15] O. Prakash, D. K. Aneja, K. Husain, P. Lohan, P. Ranjan, S. Arora, C. Sharma, K. R. Aneja, Synthesis and biological evaluation of dihydroindeno and indeno [1,2-e] [1,2,4]triazolo [3,4-b] [1,3,4]thiadiazines as antimicrobial agents, Eur. J. Med. Chem., 46 (2011) 5065-5073.