

SMOOTH DEAROMATIZATION OF SOME PHENOLS BY BAIB AND FACILE AERIAL OXIDATION OF TWO γ -HYDROGEN CONTAINING ANTHRAQUINONES.

H. N. ROY*, PIJUSH K. ROY, S. A. SHUMI, M. M. RAHMAN AND M. N. ISLAM

Department of Chemistry, Kazi Abdul Latif Research Lab., University of Rajshahi, Rajshahi-6205, Bangladesh. E-mail: hnroy01@yahoo.com

Abstract

At ambient condition bis(acetoxy)iodo benzene (BAIB) oxidized phenol and substituted phenols and the oxidized products undergo easy annulation reaction with cyanophthalide at ice cold temperature. Methyl or ethyl group at position C-1 in anthraquinone system has participated smooth aerial oxidation under sunlight.

Introduction

Quinone monoketals are used as intermediates in constructing various natural products.¹ Recent work in synthesizing angucyclines², brasiliquinones³ and deoxyrabelomycin has utilized some monoketals with necessary substituents at various positions. Thus, generation of monoketals or enones in constructing different tetracycles / pentacycles by Diels-Alder and MIRC (Michael Initiated Ring Closure) methods are essential. Oxidation of phenols generally afford monoketals or enones and are usually done by various chemical means. In most of the cases, toxic metals⁴ were used and the adopted methods are lengthy. So, today, popularly known BAIB [bis(acetoxy)iodo benzene], has drawn special attention to the chemists for the selective oxidation of phenols and β -naphthols.⁵ Using BAIB as a versatile oxidizing agent is addressed due to its mildness, non pollutant, selectivity in oxidation and above all simple reaction procedure.⁶ After oxidation, iodobenzene is its by-product, so, it could readily be separated by flash chromatographic techniques. In this report, we have employed BAIB to oxidize some phenols in bulk methanol and with the stoichiometric amount of allyl alcohol.

Ketals are very much prone to cyclization reaction with some specific Michael donors, like cyanophthalides, sulfone or thiophthalides.⁷ In this report special attention has paid to the cyclization of enone **1** and **2** in view to oxidize the cyclized products under sunlight in the presence of air.

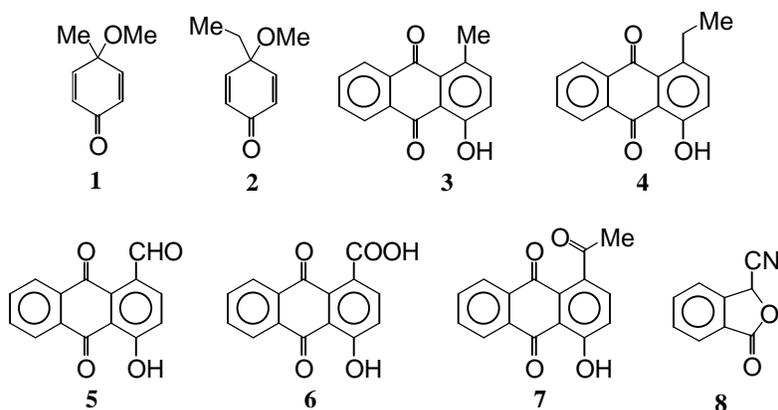
Experimental

General method for BAIB oxidation

To a stirred solution of *p*-cresole (100 mg, 0.93 mmol) in dry MeOH (5 cm³) at 0°C under CaCl₂ guard tube, BAIB (530 mg, 0.926 mmol) was added at a time. After 15 minute, the reaction was allowed to stir at room temperature over 3~4 h. Then bulk methanol was removed under reduced pressure and the residue dissolved in CHCl₃. Usual work-up of

*Author for Corresponding ; e-mail: hnroy01@yahoo.com

the organic phase afforded an oily mass which was subjected to column chromatography (pet. ether / CHCl_3 ; 8:1) on silica gel to give **1** as an oily liquid (0.079g, 68%). For allyloxy monoketals, allyl alcohol was taken in CH_2Cl_2 solvent as stoichiometric amount and the reaction was conducted at ice cold temperature.



Characterization of reaction products

The melting points were determined onto a capillary melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded using KBr pellets for solids and neat for liquids on FTIR-8400 Perkin-Elmer 883 grating spectrometer. ^1H NMR spectra were taken on AC-Bruker 200 MHz spectrometer in CDCl_3 , containing TMS as internal standard. All J values are given in Hz , chemical shifts in δ -units. MeOH was simply distilled over CaO and THF over KOH and Na-Metals. Reactions were monitored by tlc and column chromatography were carried out on 60-120 mesh (E-Merck) silica gel. BAIB were purchased from the Aldrich Chemicals.

Data for compound 1

An oily liquid; IR (neat): 1683, 1652 cm^{-1} ; ^1H NMR (CDCl_3): 6.75 (dd, 2H, $J = 4, 6, 2 \times =\text{CH}$), 6.31 (dd, 2H, $J = 4, 6, 2 \times =\text{CH}$), 3.20 (s, 3H, -OMe), 1.42 (s, 3H, - CH_3).

Data for compound 2

An oily liquid; IR (neat): 1689, 1649 cm^{-1} ; ^1H NMR (CDCl_3): 6.73 (dd, 2H, $J = 4.2, 6, 2 \times =\text{CH}$), 6.30 (dd, 2H, $J = 4.2, 6, 2 \times =\text{CH}$), 3.21 (s, 3H, -OMe), 2.31 (q, 2H, $J = 8, -\text{CH}_2$), 1.13 (t, 3H, $J = 8, -\text{CH}_3$).

Data for compound 9

An oily liquid; IR (KBr): 1681, 1653, 1657 cm^{-1} ; ^1H NMR (CDCl_3): 6.16 (d, 2H, $J = 7.8$, 2 x ring =CH), 5.72-5.68 (m, 1H, =CH), 5.66 (d, 2H, $J = 7.8$, 2 x ring =CH), 5.05-5.00 (m, 1H, =CH), 4.99-4.94 (m, 1H, =CH), 4.17-4.10 (m, 2H, $-\text{CH}_2$) 1.40 (s, 3H, $-\text{CH}_3$).

Data for compound 10

Clear liquid; IR (KBr): 1683, 1651, 1653 cm^{-1} ; ^1H NMR (CDCl_3): 6.16 (d, 2H, $J = 7.8$, 2 x ring =CH), 5.75-5.71 (m, 1H, =CH), 5.66 (d, 2H, $J = 7.8$, 2 x ring =CH), 5.09-5.04 (m, 1H, =CH), 4.98-4.93 (m, 1H, =CH), 4.15-4.11 (m, 2H, $-\text{CH}_2$), 1.91 (q, 2H, $J = 5.8$, $-\text{CH}_2$), 1.31 (t, 3H, $J = 5.8$, $-\text{CH}_3$).

Data for compound 11

Clear liquid; IR (KBr): 1681, 1655 cm^{-1} ; ^1H NMR (CDCl_3): 6.16 (d, 1H, $J = 7.8$, ring =CH), 5.66 (d, 1H, $J = 7.8$, ring =CH), 5.44 (d, 1H, $J = 7.8$, ring =CH), 3.27 (s, 6H, 2 x $-\text{OCH}_3$), 1.91 (s, 3H, $-\text{CH}_3$).

Data for compound 12

An oily liquid; IR (KBr): 1681, 1654, 1653 cm^{-1} ; ^1H NMR (CDCl_3): 6.16 (d, 1H, $J = 7.8$, ring =CH), 5.76-5.71 (m, 2H, 2 x =CH), 5.66 (d, 1H, $J = 7.8$, ring =CH), 5.44 (d, 1H, $J = 1.2$, ring =CH), 5.07-5.02 (m, 2H, 2 x =CH), 4.97-4.93 (m, 2H, 2 x =CH), 4.15-4.10 (m, 4H, 2 $-\text{CH}_2$), 1.91 (s, 3H, $-\text{CH}_3$); HRMS: calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_3$ 220.2706 found 220.2707.

Data for compound 13

Clear liquid; IR (KBr): 1680, 1651 cm^{-1} ; ^1H NMR (CDCl_3): 6.10 (d, 1H, $J = 7.8$, ring =CH), 5.94-5.89 (m, 1H, ring =CH), 5.66 (d, 1H, $J = 7.8$, ring =CH), 3.25 (brs, 6H, 2 x $-\text{OCH}_3$), 1.43 (s, 3H, $-\text{CH}_3$).

Data for compound 14

An oily liquid; IR (KBr): 1690, 1584, 1583 cm^{-1} ; ^1H NMR (CDCl_3): 6.01 (d, 1H, $J = 7.8$, ring =CH), 5.91-5.82 (m, 1H, ring =CH), 5.76-5.68 (m, 2H, 2 x =CH), 5.66 (d, 1H, $J = 7.8$, ring =CH), 5.17-5.11 (m, 2H, 2 x =CH), 4.99-4.91 (m, 2H, 2 x =CH), 4.15-4.10 (m, 4H, 2 x $-\text{CH}_2$), 1.81 (s, 3H, $-\text{CH}_3$). HRMS: calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_3$ 220.2707 found 220.2704.

Data for compound 15

An oily liquid; IR (KBr): 1683, 1657 cm^{-1} ; ^1H NMR (CDCl_3): 6.70 (d, 2H, $J = 7.8$, 2 x ring =CH), 6.47 (d, 2H, $J = 7.8$, 2 x ring =CH), 4.04 (s, 3H, $-\text{OCH}_3$). HRMS: calcd. for $\text{C}_7\text{H}_7\text{O}_2\text{Br}$ 202.0509 and 204.0507 found 202.0507 and 204.0509.

Data for compound 16

An oily liquid; IR (KBr): 1687, 1654, 1647 cm^{-1} ; ^1H NMR (CDCl_3): 6.65 (d, 2H, $J = 7.8$, 2 x ring =CH), 6.46 (d, 2H, $J = 7.8$, 2 x ring =CH), 5.93-5.86 (m, 1H, =CH), 5.24-5.17

(m, 1H, =CH), 5.21-5.12 (m, 1H, =CH), 4.11-4.02 (m, 2H, -CH₂). HRMS: calcd. for C₉H₆O₂Br 228.0891 and 230.0871 found 228.0893 and 230.0872.

Data for compound 17

Oily liquid; IR (neat): 1683, 1639 cm⁻¹; ¹H NMR (CDCl₃): 7.56 (dd, 1H, *J* = 2.2, 6.4, Ar-H), 7.29-7.19 (m, 2H, 2 x Ar-H), 7.15-7.09 (m, 2H, Ar-H & =CH), 5.95 (d, 1H, *J* = 10, =CH), 3.19 (brs, 6H, 2 x -OMe).

Data for compound 18

An oily liquid; IR (KBr): 1685, 1643, 1651 cm⁻¹; ¹H NMR (CDCl₃): 7.64 (d, 1H, *J* = 7.8, ring =CH), 7.23-7.07 (m, 4H, Ar-H), 6.40 (d, 1H, *J* = 7.8, ring =CH), 5.91-5.86 (m, 2H, 2 x =CH), 5.26-5.21 (m, 2H, 2 x =CH), 5.27-5.22 (m, 2H, 2 x =CH), 4.09-4.02 (m, 4H, 2 x -CH₂).

General method for annulation of compound 3

To a stirred solution of lithium *tert*-butoxide (LiOBu^t) (0.0127g, 0.158 mmol) in dry THF (5 cm³) under N₂ atmosphere and at ice cold temperature, cyanophthalide (0.025g, 0.158 mmol) was added to it. After 5 minute (a pale yellow colour developed at this stage), enone **1** (0.025g, 0.181 mmol) with THF (3 cm³) was added drop-wise (over 1 min.) to the reaction mixture. A deep blue colour solution was appeared at this stage and the resulting mixture was kept at 0°C to additional 15 minute. Later it was kept at room temperature over 3 h and a tlc was monitored to ensure the end of the reaction. The reaction mixture was then quenched by saturated NH₄Cl solution and THF was removed under vacuo. A deep orange-red solid was formed over water and it was separated by CHCl₃ extraction. Organic extract was washed by brine, dried over Na₂SO₄ and then evaporation to give an orange solid. Quick column chromatographic separation of this solid by CHCl₃ / pet. ether (2:1) eluents furnished an orange-red compound **3** with 82% (0.039 g) yield.

Data for compound 3

M.p. 172-173°C; IR (KBr): 3446, 1743, 1629 cm⁻¹; ¹H NMR (CDCl₃): 13.17 (s, 1H Ar-OH), 8.31-8.25 (m, 2H, 2 x Ar-H), 7.82-7.77 (m, 2H, 2 x Ar-H), 7.49 (d, 1H, *J* = 8, Ar-H), 7.22 (d, 1H, *J* = 8, Ar-H), 2.43 (s, 3H, Ar-CH₃); HRMS: calcd. for C₁₅H₁₀O₃ 238.2451 found 238.2452.

General method for photochemical reaction

Compound **3** (25 mg, 0.1 mmol) was dissolved into distilled CHCl₃ (5 cm³) and catalytic amount of AIBN (0.01 mol%) was added to it. This resulting mixture was exposed to sunlight over 5-6 h. After completion (monitored by tlc) of the reaction, it was concentrated and chromatographed to give **5** (14 mg, 52%) and **6** (13 mg, 48%). For compound **4** the same reaction procedure was followed without AIBN.

Data for compound 5

M.p. 157-158°C; IR (KBr): 3429, 1689, 1637, 1584 cm^{-1} ; ^1H NMR (CDCl_3): 12.90 (s, 1H, Ar-OH), 9.15 (s, 1H, -CHO), 8.12-8.05 (m, 2H, 2 x Ar-H), 7.74-7.71 (m, 2H, 2 x Ar-H), 7.60 (d, 1H, $J = 8.4$, Ar-H), 7.12 (d, 1H, $J = 8.4$, Ar-H); HRMS: calcd. for $\text{C}_{15}\text{H}_8\text{O}_4$ 252.2286 found 252.2287.

Data for compound 6

Orange colour crystal; m.p. 234-236°C (Lit.⁸ 240-241°C); IR (KBr): 3410, 1633, 1584 cm^{-1} , ^1H NMR (d_6 -DMSO): 12.80 (s, 1H, Ar-OH), 8.27-8.07 (m, 2H, 2 x Ar-H), 7.78-7.73 (m, 2H, 2 x Ar-H), 7.59 (d, 1H, $J = 8.4$, Ar-H), 7.25 (d, 1H, $J = 8.4$, Ar-H); HRMS: calcd. for $\text{C}_{15}\text{H}_8\text{O}_5$ 268.2280 found 268.2281.

Data for compound 7

Orange colour crystal; m.p. 182-183 °C; IR (KBr): 3435, 1697, 1633, 1587 cm^{-1} ; ^1H NMR (CDCl_3): 13.13 (s, 1H, Ar-OH), 8.17-8.01 (m, 2H, 2 x Ar-H), 7.79-7.74 (m, 2H, 2 x Ar-H), 7.49 (d, 1H, $J = 8.4$, Ar-H), 7.15 (d, 1H, $J = 8.4$, Ar - H), 2.13 (s, 3H, - CH_3). HRMS: calcd. for $\text{C}_{16}\text{H}_{10}\text{O}_4$ 266.2557 found 266.2558.

Results and Discussion

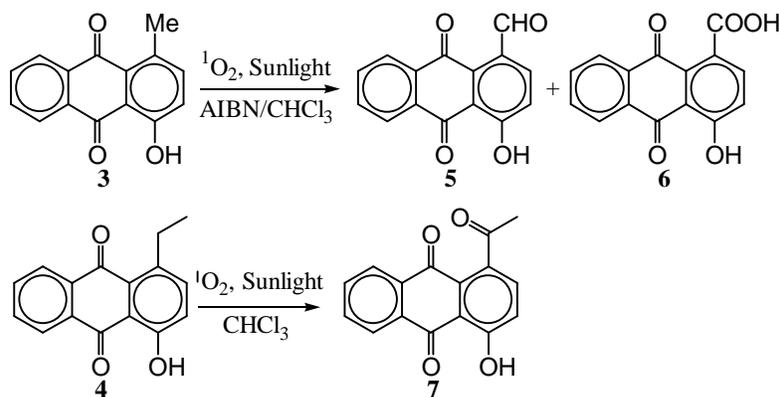
Bis(acetoxy)iido benzene is a versatile and specific oxidant to phenols and β -naphthols containing electron releasing substituents in the ring. In one of our work⁹ we have synthesized few ketals with methanol and cyclized them with thiophthalide or cyanophthalide **8** and obtained higher yield. With the intention of cyclization and subsequent photooxygenation reaction to compound **3** and **4** some phenols (entry I - VI) were oxidized to monoketals (Table 1). All phenols underwent smooth oxidation with BAIB, except *o* / *p*-nitrophenol, *o* / *p*-hydroxybenzoic acid and their esters. Structures of enones were established by IR, NMR and in some cases mass spectroscopic method have been utilized. Generally, for all the enones two IR peaks at $\bar{\nu} = 1668, 1624 \text{ cm}^{-1}$ has been detected for $>\text{C}=\text{O}$ and double bonds respectively. In the ^1H NMR spectroscopy, protons for double bonded -CH were detected in the region 6.75 ~ 6.30 ppm. Mass spectroscopic data also supported the formation of those monoketals. Unfortunately, some phenols having electron withdrawing substituents did not participate in BAIB oxidation even in reflux condition. Our apprehension may be the presences of electron withdrawing groups in phenol ring are responsible of this failure. Even ester of the phenolic acid did not undergo BAIB oxidation. As a test case, allyl alcohol was reacted with phenol to make some allyl ketals by the same oxidant BAIB. Notably, allyl alcohol has taken part in dearomatization reaction beautifully with phenol but the reaction time was relatively higher and the reaction happened at ice cold temperature. We have observed allyloxy containing ketals are sensitive towards heat and light, so these ketals were stored in the refrigerator. All the allyloxy substituted ketals were characterized by the same spectroscopic methods and the allylic protons were detected at 4.17 ~ 4.10 ppm in ^1H NMR spectra. Total number of protons and specially the presence of allylic protons have clearly indicated the formation of allyloxy enones.

Table 1.

Entry	Starting phenol	Oxidant	Reactant alcohol	Time / solvent	Product	Yield (%)
I		BAIB	Methanol	4 h MeOH	 1	68
		BAIB	Allyl alcohol	4 h CH ₂ Cl ₂	 9	52
II		BAIB	Methanol	4 h MeOH	 2	62
		BAIB	Allyl alcohol	6 h CH ₂ Cl ₂	 10	50
III		BAIB	Methanol	4 h MeOH	 11	69
		BAIB	Allyl alcohol	4 h CH ₂ Cl ₂	 12	54
IV		BAIB	Methanol	4 h MeOH	 13	69
		BAIB	Allyl alcohol	4 h CH ₂ Cl ₂	 14	52
V		BAIB	Methanol	4 h MeOH	 15	54
		BAIB	Allyl alcohol	4 h CH ₂ Cl ₂	 16	49
VI		BAIB	Methanol	4 h MeOH	 17	64
		BAIB	Allyl alcohol	4 h CH ₂ Cl ₂	 18	54

In view to obtain anthraquinone system with γ -hydrogen in A-ring, enone **1** & **2** have subjected to annulation reaction with cyanophthalide **8**. From a known procedure,¹⁰ cyanophthalide was prepared from phthalaldehydic acid and aqueous KCN. Under N₂ atmosphere and in the presence of LiOBu^t, cyanophthalide underwent smooth annulation reaction with enone **1** at ice cold temperature. Spectroscopic data has clearly demonstrated the formation of compound **3**.

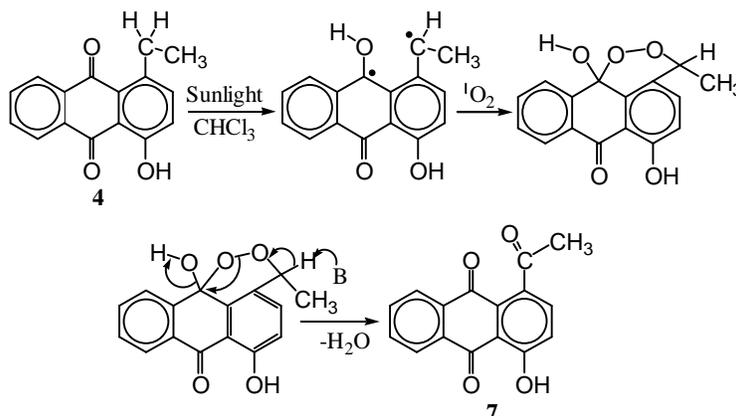
Methyl group in compound **3** contains three γ -hydrogen atom at C-1 Carbon. Normally, we could expect a photochemical reaction (Norrish type-II) at that methyl carbon. In view to adopt the advantages of this reaction, CHCl₃ solution of compound **3** was kept in open sunlight. After prolong exposure in sunlight, compound **3** did not change at all (monitored by tlc). So, we have added a tiny crystal of Cu(I) salt to this solution to initiate free radical generation in compound **3**. Unfortunately, no significant changes of compound **3** were found in tlc. Our apprehension, free radical generation is not possible for compound **3** by sunlight because the methyl group at C-1 rotate at a very faster rate which causes proton abstraction difficult by C-9 carbonyl group. So in the presence of air (¹O₂, singlet oxygen), cyclic peroxide did not form at all. Therefore to promote the radical generation in compound **3** we have added AIBN (0.01 mol%) into the CHCl₃ solution. By this technique within 4 hour, two new spots were detected in tlc. After separation and subsequent purification, compound **5**, **6** were obtained in good yield. Spectroscopic data clearly indicated the formation of an aldehyde **5** and an acid **6**. According to reaction mechanism, initially compound **5** was formed and thereafter in the presence of air and AIBN, compound **5** further oxidized to compound **6**.



Scheme 1.

On the contrary, in sunlight, compound **4** gave the product **7** without AIBN. We thought compound **4** in the presence of sunlight can generate free radical quickly and thereby trap the singlet oxygen (¹O₂) and formed cyclic peroxide. Because the derived free radical from compound **4** is secondary in nature and therefore it is readily formed by sunlight. Thus the reaction mechanism (Scheme 2) delineated the unambiguous settlement of

>C=O group in place of methylene for compound **4**. In addition, spectroscopic data also supported the formation of ketone **7**.



Scheme 2.

The above oxidation can be done by molecular oxygen under basic condition or by CrO_3 oxidation.¹⁰ But the present photochemical introduction of oxygen at the benzylic carbon (C-1) is quite simple, mild and environmentally benign.

Conclusion

In this report several enones or ketals were prepared in moderate to good yield with methanol and allyl alcohol by a mild, non pollutant oxidant, BAIB. Cyclization and subsequent aerial oxidation of compound **3** by AIBN in sunlight gave two products **5**, **6** and the compound **4** gave product **7** in excellent yield. Any system that contains γ -hydrogen with respect to >C=O group at C-1 in anthraquinone system that can participate smooth aerial oxidation under sunlight. Undoubtedly, this easy aerial oxidation method could open a new site for the chemical transformations of various anthraquinones into other important products.

Acknowledgement

The authors are grateful to Ashis Kumer Sarker a Ph.D fellow in South Korea, for IR, NMR and MS spectra and to the Department of Chemistry, University of Rajshahi, for the assistance of various chemicals.

References

- (a) J. S. Swenton, *Acc. Chem. Res.*, 1983, **16**, 74.
 (b) D. R. Henton, K. Anderson, M. J. Manning and J. S. Swenton, *J. org. Chem.*, 1980, **95**, 3422.
 (c) H. Musso, *Angew. Chem.*, 1963, **75**, 965.

- (d) T. Kametani and K. Fukumoto, *Synthesis*, 1972, 657.
2. (a) A. S. Mitchell and R. A. Russel, *Tetrahedron.*, 1997, **53**, 4387.
(b) A. S. Mitchell and R. A. Russel, *Tetrahedron.*, 1995, **51**, 5207.
3. (a) H. N. Roy, D. Mal, N. K. Hazra and S. Adhikari, *Tetrahedron.*, 1997, **53**, 2177.
(b) H. N. Roy and D. Mal, *J. Chem. Soc., Perkin Trans-1*, 1999, 3167.
4. (a) M. A. Schwartz and I. S. Mami, *J. Am. Chem. Soc.*, 1975, **97**, 1239.
(b) J. Brussee and A. C. Jansen, *Tetrahedron Lett.*, 1983, 3261.
5. (a) A. Pelter and S. M. A. Elgendy, *J. Chem. Soc., Perkin Trans 1*, 1993, 1891.
(b) U. K. Mallik and A. K. Mallik, *Ind. J. Chem. Sec B.*, 1991, **30B**, 611.
(c) H. N. Roy, M. S. Sarkar and D. Mal, *Synth. Commun.*, 2005, **35**, 2183.
6. A. S. Mitchell and R. A. Russel, *Tetrahedron Lett.*, 1993, **34**, 545.
7. F. M. Hauser and D. Mal, *J. Am. Chem. Soc.*, 1984, **106**, 1862.
8. W. H. Bentley, H. D. Gardener and C. Weizmann, *J. Chem. Soc.*, 1907, **91**, 1625.
9. H. N. Roy, S. K. Ghorai, M. Bandopadhaya and D. Mal, *J. Chem. Res. (S)*, 1999, 30.
10. (a) G. A. Krauss and H. Sugimoto, *Tetrahedron Lett.*, 1978, 2263.
(b) F. A. Hauser and R. P. Rhee, *J. Org. Chem.*, 1978, **43**, 178.

(Received :20 October, 2010; Accepted: 8 October, 2011)