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Studies on Copper(I) Catalysed Cross-Coupling Reactions : A Convenient and Facile Method for the Synthesis of Diversely Substituted α ,β -Acetylenic Ketones[1]

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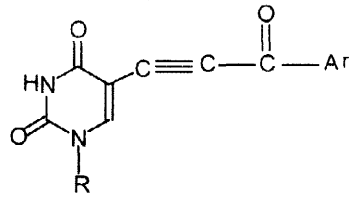
Abstract: Terminal alkynes reacted with acid chlorides in the presence of cuprous iodide as a catalyst in Et_3N at room temperature yielding a number of α, β-acetylenic ketones in good to excellent yields.

Organic synthesis has benefited enormously as a result of commendable discoveries in the field of transition metal catalysed organic transformations. Among the transition metals, copper(I) has been utilised efficiently as catalyst over the years for many important useful synthetic transformations[2]. Inspired by spectacular advances in the domain of this particular transition metal catalysed synthesis, we embarked upon a systematic study of copper(I) catalysed acylation of terminal alkynes which led to the formation of α ,β-acetylenic ketones efficiently.

α,β-Acetylenic ketones are of considerable interest because of their widespread occurrence among natural products and their physiological properties.[3] Recently, uracil **I** and its corresponding nucleosides **II** and **III** substituted at C-5 position by an acetylenic ketone functionality displayed promising cytotoxic activities against CCRF-CEM human lymphoblastoid cells and L1210 mouse leukemia cells in culture.[4,5] These compounds were also shown to be inhibitors of thymidylate synthase , an essential enzyme needed for cellular multiplication processes. In some cases they showed pharmacological activity similar to 5-fluorouracil, a classical drug that has found application in clinical cancer chemotherapy.[6] Other acetylenic compounds have been used in the synthesis of various types of biologically important C-nucleosides[7] and in various carboannulation[8] and heteroannulation processes.[9]



I R = H

II R = 2'-deoxy-D-erythro-pentafuranose

III R = $-CH_2-O-(CH_2)_2-OH$

Because of their occurrence in nature and their promising biological activity, various classical methods have been developed for the synthesis of α ,β -acetylenic ketones.[10] Recent progress has been made through the development of methods which involved palladium catalysed reactions of (a) 1-alkynes with acyl chlorides,[11a] (b) of 1-alkynes with aryl or vinyl halides in presence of carbon monoxide[11b] (c) acylation of alkynyl zincs[11c] and alkynyl stannanes[11d] with acyl chlorides. However, all of these reactions involve either costly palladium catalyst or the metal salts derived from zinc, tin or silicon which are difficult to be prepared and cause some times side reactions. Recently, Zanina and co-workers[12] have reported a method for the synthesis of α, β-acetylenic ketones from terminal alkynes and acid chlorides using cuprous iodide as a catalyst. However the reaction was carried out in toluene as a solvent at elevated temperature and only one alkyne e.g. phenyl acetylene was studied. Later the reaction was adopted by Brown and co-workers.[13] However, because of the use of high temperature and toluene as a solvent, we found Zanina's method to be

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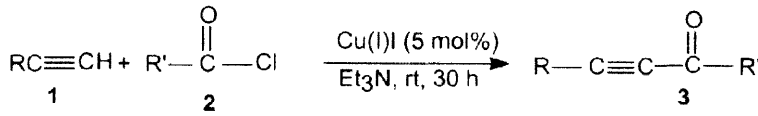
inadequate for the synthesis of a number of acetylenic ketones we needed for our biological studies. We found that the use of triethylamine as a solvent and also as a base obviated many of the difficulties and the reactions could be carried out at room temperature successfully. This paper describes a detailed procedure for the synthesis of α,β -acetylenic ketones, by using cuprous iodide as a catalyst.

Results and Discussion

Recently we have studied palladium catalysed heteroannulation reactions where bis(triphenylphosphine)palladium chloride was used as a catalyst with cuprous iodide as co-catalyst.[14] We now report that acylation of terminal alkynes can be effected in the presence of copper(I) iodide (5 mol%) alone without the need for any palladium catalyst[11a] in triethylamine as a solvent as shown in Scheme 1.

Scheme 1



1 2 3

The reactions were generally carried out at room temperature for 30 h. while the use of higher temperature did not lead to any improvement in yields. Alkynes used in this synthetic protocol were either purchased or synthesised.[15] 5-Ethynyl-2,4-dimethoxypyrimidine (**1d**) was synthesised according to the known literature procedure.[16] The acid chlorides were synthesised from the corresponding acids using phosphorous pentachloride or thionyl chloride.[17]

Copper(I) iodide (5 mol%) was found to be the optimum amount of catalyst (see Table 1, entry 1 & 2). Other copper halides e.g. Cu(I)Cl, or Cu(I)Br showed less reactivity in their product yields (20-40%). Amongst various bases (diethylamine, triethylamine, pyrrolidine, butylamine, potassium carbonate/tetrabutylammonium chloride) triethylamine was found to be most effective and it was used as a base as well as a solvent. Yields were found generally good to excellent (except entry 5). The products are highly stable and can be stored under room temperature except product **3i**. The product **3i** decomposed upon exposure to heat and light. However, it could be stored in the dark at low temperature.

Both alkyl, aryl or heteroaryl substituted acetylenic compounds have been utilised successfully for the synthesis of α,β-acetylenic ketones. As can be seen from Table I, aryl acetylenes gave better yields than alkyl acetylenes (Table-I, entry 2 vs. 11). The reaction was found to be tolerant of other functional groups [e.g. hydroxy (entry 11), methoxy (entry 9) and silyl (entry 10)]. The reaction could be carried out with a variety of aromatic and aliphatic acid chlorides (entries 2 vs. 5, Table - I). However, straight chain aliphatic acid chlorides (e.g. acetyl, propionyl and butyryl chlorides) did not work under our reaction condition. We observed that when straight chain aliphatic acid chlorides were added to the reaction mixture, an exothermic reaction took place and the whole reaction mixture was converted into a black tar immediately. It is noteworthy that acid chlorides having electron withdrawing and donating group (see entries 2 and 4, Table - I) are equally effective for this reaction. However, when 2-chloro-5-nitrobenzoyl chloride was employed, no desired product **3** could be isolated presumbly due to steric factor.

By tlc, the acetylenic ketones were slower moving than the corresponding starting materials. All of the products **3** were well characterised by spectral evidences (IR, UV, ^{1}H and ^{13}C NMR, mass spectra) and elemental analyses. In IR spectra, acetylenic ketones exhibited strong absorption at 2100-2210 cm^{-1} (for carbon-carbon triple bond) and 1600-1650 cm^{-1} (for ketone). In ^{1}H NMR, typically for product **3j**, the two methyl protons appeared as singlet at around δ 1.68 and the other methyl group attached with the benzene ring appeared as another singlet at around δ 2.4. A broad singlet appeared at δ 3.64 due to the -OH group. The ortho protons of the benzene ring appeared as clean doublets (J=8 Hz) around δ 8.06 and δ7.26 respectively.

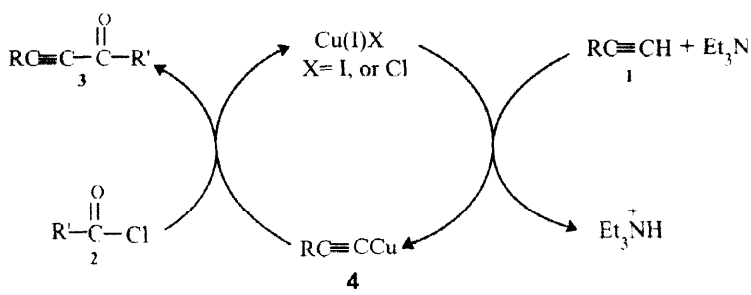
Table 1. Synthesis of α , β-acetylenic ketones through copper(I) catalysed acylation of terminal alkynes[a]

Entry	Acetylenes 1 R	Acid Chlorides 2 R'	Product 3	yields[b](%)
1[c]	Phenyl **1a**	C_6H_4Me-p **2a**	**3a**	0
2.	Phenyl **1a**	C_6H_4Me-p **2a**	**3a**	83
3.	Phenyl **1a**	Phenyl **2b**	**3b**	78
4.	Phenyl **1a**	$C_6H_4NO_2$-p **2c**	**3c**	82
5.	Phenyl **1a**	$(CH_3)_2CH$ **2d**	**3d**	48
6.	Phenyl **1a**	$ClCOC_6H_4COCl$ **2e**	**3e**	61
7.	n-butyl **1b**	**2e**	**3f**	63
8.	1-naphthyl **1c**	C_6H_4Cl-p **2f**	**3g**	62
9.	2,4-dimethoxy pyrimidine-5-yl **1d**	C_6H_4Me-p **2a**	**3h**	65
10.	$SiMe_3$ **1e**	**2a**	**3i**	79
11.	$(CH_3)_2C(OH)$ **1f**	**2a**	**3j**	71

[a]Reactions were carried out in dry Et_3N with terminal alkynes (3 mmol), copper(I) iodide (0.15 mmol) and acid chloride (3.75 mmol) at room temperature for 30 h.
[b]Yields were determined based on terminal alkynes after the isolation of spectroscopically pure products using column chromatography.
[c]Entry 1 was carried out without copper(I) iodide.

Mechanistically this reaction could be envisaged to involve the following steps (Scheme - 2).

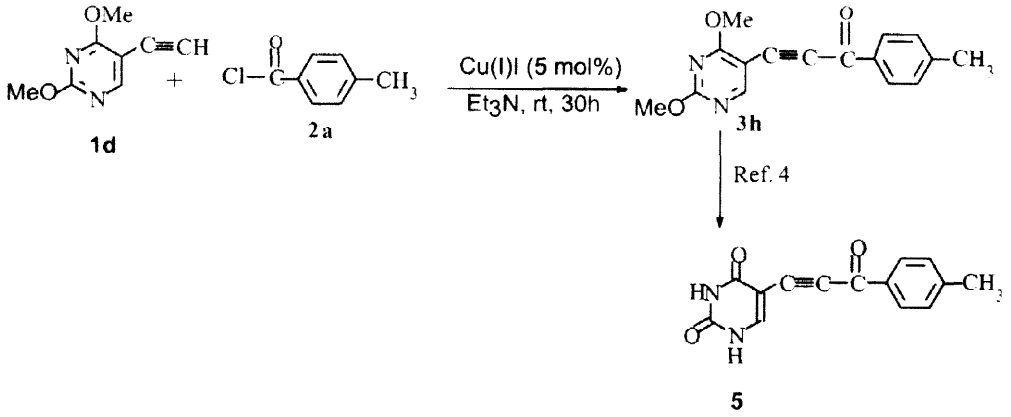
Scheme 2



(i) The copper salts (**4**) of the alkynes are formed from the terminal alkynes in the presence of cuprous iodide[18] and triethylamine (base), (ii) The reaction of copper acetylides with the acid chlorides lead to the formation of the acetylenic ketones **3** and copper(I) chloride which could participate in the catalytic cycle again. It should be pointed out that this process is free from dimers of the acetylenic compounds which are usually formed in palladium catalysed reactions[19] of terminal alkynes.

This method has also been applied for the synthesis of a uracil derivative **5** containing the α,β-acetylenic ketone moiety (Scheme- 3) which is of potential biological importance.

Scheme 3



Thus we have described a very simple but an efficient method for the synthesis of α ,β -acetylenic ketones from readily available starting materials. Although, a similar type of method was reported by Zanina and co-workers, however, the reaction was limited due to use of toluene as a solvent at elevated temperature. Our method differs significantly in the use of triethylamine as base as well as solvent at room temperature using a spectrum of alkynes and acid chlorides establishing its versatility. We have also carried out the study in fuller details. Moreover, it is certainly superior to the methods which involve the use of metal salts of alkynes[10d,11c] or their silylated[10a,b] or stannyl derivatives.[11d] We believe the method will find significant application in organic synthesis.

Experimental

Melting points were determined on Reichert (285980), Austria melting point apparatus and were uncorrected. All catalyst and co-catalyst used were commercially available. Solvents and reagents were purified by conventional methods. The petroleum ether used is the fraction boiling at 60-80^{0}C. Ether refers to diethyl ether. Silica gel TLC was performed on 60F-254 precoated sheets. Column chromatography was carried out on silica gel (60-120 mesh). The acid chlorides were synthesised from the corresponding acids using phosphorous pentachloride or thionyl chloride. Acetylenic compounds were either commercially available or, synthesised according to the known literature procedures.

The UV spectra were recorded in spectrophotometric grade ethanol (Baker). The IR spectra were taken as KBr plates. ^{1}H NMR in $CDCl_3$ solutions were recorded at 60 MHz or 100 MHz or 300 MHz. ^{13}C NMR spectra were recorded at 75 MHz.

General method for the synthesis of α ,β -acetylenic ketones 3. To a well-stirred mixture of acetylenic compound **1** (3 mmol) and copper(I) iodide (0.15 mmol) in Et_3N (9 ml) was added the acid chloride **2** (3.75 mmol). The whole reaction mixture was stirred at room temperature for 30 h under an oxygen free argon atmosphere. At the end of the reaction, triethylamine was removed under reduced pressure and the residue was treated with methanol (3 ml). After the removal of methanol, the whole reaction mixture was extracted with chloroform (3x75 ml). The combined extracts were washed with water (2x50 ml). The solvent was removed under vacuum and the crude product **3** was purified by column chromatography on silica gel.

3-Phenyl-1-(p-tolyl)-2-propyn-1-one (3a) : yield 83%; m.p. 86-88°C (petroleum ether); IR (KBr) : ν_{max} 2205, 1640, 1605 cm^{-1}; UV (EtOH) : λ_{max} 289 (logε 4.2); ^{1}H NMR (60 MHz, CCl_4) :δ 2.46 (s, 3H, -CH_3), 7.26-7.83 (m, 7H, Ar-H), 8.13 (d, J = 8 Hz, 2H, Ar-H); Anal. Calcd. for $C_{16}H_{12}O$: C, 87.25; H, 5.49. Found : C, 87.56; H, 5.73.

1,3-Diphenyl-2-propyn-1-one (3b) : yield 78%; colourless thick oil (lit.[2a,12] oil); IR (neat) ν_{max} 2200, 1640, 1600 cm^{-1}; UV (EtOH) : λ_{max} 289 (log ε 4.16); ^1H NMR (60 MHz, CCl_4) δ 7.33-7.92 (m, 8H, Ar-H), 8.15-8.26 (m, 2H, Ar-H).

1-(p-Nitrophenyl)-3-phenyl-2-propyn-1-one (3c) : yield (82%), mp 162-163°C (lit[12] 162-163°C); IR (KBr)ν_{max} 2200, 1650, 1600, 1520 cm^{-1}; UV (EtOH) : λ_{max} 308.6 (logε 4.18), 271 (log ε 4.21), 205 (log ε 4.36); ^1H NMR (60 MHz, $CDCl_3$) δ 7.49-7.86 (m, 5H, Ar-H), 8.49 (s, 4H, Ar-H).

4-Methyl-1-phenyl-1-pentyn-3-one (3d) : colourless liquid, yield (48%) (lit[13] oil), IR (neat) ν_{max} 2200, 1650, 1600 cm^{-1}; UV (EtOH) : λ_{max} 284.6 (log ε 4.14); ^1H NMR (60 MHz, CCl_4) δ1.23 (d, J = 6 Hz, 6H, -$2CH_3$), 2.66 (m, 1H, $CH(CH_3)_2$), 7.33-7.73 (m, 5H, Ar-H).

1,4-Bis(3-phenylprop-2-ynoyl)benzene (3e) : light yellow solid (ether/petroleum ether); yield 54%; m.p. 188-190°C; IR (KBr) : ν_{max} 2200, 1630, 1590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)δ 7.28-7.53 (m, 6H, Ar-H), 7.73 (d, J = 6 Hz, 4H, Ar-H), 8.36 (s, 4H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 Mhz) δ_c 87.23, 94.95, 120.14, 129.21, 130.07, 131.60, 133.64, 140.91, 177.49; Anal. Calcd. for $C_{24}H_{14}O_2$: C, 86.20; H, 4.22. Found : C, 86.12; H, 3.94.

1,4- Bis(hept-2-ynoyl)benzene (3f) : colourless liquid; yield 50%; IR (neat) ν_{max} 2200, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 300 Mhz) δ_H 0.90 (t, J = 6 Hz, 6H, -CH_3), 1.34-1.50 (m, 4H, -CH_2), 1.56-1.65 (m, 4H, -CH_2), 2.46 (t, J = 6 Hz, 4H, -CH_2-C-), 8.14 (s, 4H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_c 13.90, 19.37, 22.49, 30.16, 80.06, 98.74, 129.90, 140.78, 177.75. Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.59; H, 7.53. Found : C, 81.37; H, 7.46.

1-(p-Chlorophenyl)-3-naphthyl-2-propyn-1-one (3g) : yield 62%; white solid, m.p. 115-116°C (petroleum ether); IR (KBr) : ν_{max} 2200, 1640, 1600 cm^{-1}; UV (EtOH) λ_{max} 351.6 (log ε 4.2), 273 (log ε 4.3), 223 (log ε 4.74); ^1H NMR (60 MHz, CCl_4) δ 7.33-8.5 (m, 11H, Ar-H); MS m/e (rel. intn.) 291 (M^+, 100), 274(15), 262(30), 239(30), 226(30). Anal. Calcd. for $C_{19}H_{11}OCl$: C, 78.48; H, 3.81. Found : C, 78.35; H, 4.12.

3-(2,4-Dimethoxypyrimidin-5-yl)-1-(p-tolyl)-2-propyn-1-one (3h) : yield 65%; light yellow solid; m.p. 138-140°C (lit[4] 140-141°C); IR (KBr) : ν_{max} 2950, 2200, 1635, 1595 cm^{-1}; UV (EtOH) λ_{max} 322 (log ε 4.39); ^1H NMR (100 MHz, $CDCl_3$) δ 2.44 (s, 3H, Ar-CH_3), 4.04 (s, 3H, -OCH_3), 4.12 (s, 3H, -OCH_3), 7.32 (d, 2H, J = 8 Hz, Ar-H), 8.13 (d, 2H, J = 8.0 Hz, Ar-H), 8.56 (s, 1H, -C_6-H of pyrimidine ring).

1-(p-Tolyl)-3-trimethylsilyl)-2-propyn-1-one (3i) : colourless oil; yield 79%; IR (neat) : ν_{max}2190, 1640, 1600 cm^{-1}; UV (EtOH) : λ_{max}/nm 276 (logε 4.27), 221.9 (logε 4.10), 207 (logε 4.12); ^1H NMR (60 MHz, CCl_4) δ 0.3 (s, 9H, -$SiMe_3$), 2.43 (s, 3H, Ar-CH_3), 7.25 (d, J = 8 Hz, 2H, Ar-H), 8.0 (d, J = 8 Hz, 2H, Ar-H). Anal. Calcd. for $C_{13}H_{16}OSi$: C, 72.16; H, 7.45. Found : C, 72.11; H, 7.39.

4-Hydroxy-4-methyl-1-(p-tolyl)-2-pentyn-1-one (3j) : colourless liquid; yield 71%; IR (neat) : λ_{max} 3420, 2200, 1640, 1600 cm^{-1}; UV (EtOH) : λ_{max}/nm 274 (log 4.04), 221.0 (logε 3.93), 204 (logε 4.0); ^1H NMR (100 MHz, $CDCl_3$) δ 1.6 (s, 6H, $2CH_3$), 2.4 (s, 3H, Ar-CH_3), 3.64 (brd, 1H, -OH), 7.26 (d, J = 8 Hz, 2H, Ar-H), 8.04 (d, J = 8 Hz, 2H, Ar-H); Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.97. Found : C, 77.15; H, 6.91.

References and Notes

1. A part of the results appeared as a preliminary communication : Chowdhury, C.; Kundu, N.G. *Tetrahedron Lett.*, **1996**, *37*, 7323-7324; corrigendum : Chowdhury, C.; Kundu, N.G. *Tetrahedron Lett.*, **1997**, *38*, 1863.
2. (a) Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. *J. Org. Chem.*, 1993, *58*, 4716-4721; (b) Jeffery, T. *J. Chem. Soc., Chem. Commun.*, 1988, 909-910; (c) Jeffery, T. *Tetrahedron Lett.*, 1989, *30*, 2225-2228; (d) Alami, M. and Ferri, F. *Tetrahedron Lett.*, 1996, *37*, 2763-2766; (e) Mignani, G.; Chevalier, C.; Grass, F.; Allmang, G.; Movel, D. *Tetrahedron Lett.*, **1990**, *31*, 5161-5164.
3. (a) Faweett, C.H.; Firu, R.D.; Spencer, D.M. *Physiological Plant Pathology*, **1971**, *1*, 163. (b) Imai, K. *J. Pharm. Soc. (Japan)* **1956**, *76*, 405. (c) Drews, S.E.; Libenberg, R.W. EP 130 829, January 1985, *Chem. Abstr.* **1985**, 103, 22381X.
4. Kundu, N.G.; Das, B.; Spears, C.P.; Majumder, A.; Kang, S.-I. *J. Med. Chem.* **1990**, *33*, 1975-1979.
5. (a) Kundu, N.G.; Dasgupta, S.K. *J. Chem. Soc.; Perkin Trans. 1.* **1993**, 2657-2663; (b) Kundu, N.G.; Mahanty, J.S. and Spears, C.P. *Bioorganic and Medicinal Chemistry Lett.* **1996**, *6*, 1497-1502.

6. Heidelberger, C. *Pyrimidine and Pyrimidine Antimetabolites in Cancer Medicine*; Holland, J.F.; Frei, E.; Eds.; Lea and Febiger : Philadelphia, **1984**, pp. 801-824.
7. (a) Gupta, C.M.; Jones, G.H.; Moffat, J.G. *J. Org. Chem.* **1976**, *41*, 3000-3009; (b) Tam, S.Y.-K.; Klein, R.S.; De las Haras F.G.; Fox, J.J. *J. Org. Chem.* **1979**, *44*, 4854-4862.
8. (a) Balsubramanian, K.K.; Selvaraj, S.; Venkataramani, P.S. *Synthesis* **1980**, 29-30; (b) Wagner, F. and Meier, H. *Tetrahedron* **1974**, *30*, 773-780.
9. (a) Utimoto, K.; Miwa, H.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4277-4278; (b) Okuro, K.; Furuune, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1992**, *57*, 4754-4756; (c) Pflieger, D.; Muckensturm, B. *Tetrahedron Lett.* **1990**, *31*, 2299-2300.
10. (a) Birkofer, L.; Ritter, A.; Uhlenbrauck, H. *Chem. Ber.* **1963**, *96*, 3280-3288; (b) Walton, D.R.M.; Waugh, F. *J. Organomet. Chem.* **1972**, *37*, 45-56. (c) Chopard, P.A.; Searle, R.J.G. and Devitt, F.H. *J. Org. Chem.* **1965**, *30*, 1015-1019; (d) Brown, H.C.; Racherla, U.S.; Singh, S.M. *Tetrahedron Lett.* **1984**, *25*, 2411-2414.
11. (a) Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1977**, 777-778; (b) Arcadi, A.; Cacchi, S.; Marinelli, F.; Pace, P.; Sanzi, G. *Synlett.* **1995**, 823-824; (c) Negishi, E.-I.; Bagheri, V.; Chatterjee, S.; Luo, F.-T.; Miller, J.A.; Soll, A.T. *Tetrahedron Lett.* **1983**, *24*, 5181-5184. (d) Logue, M.W.; Teng, K. *J. Org. Chem.* **1982**, 47, 2549-2553.
12. Zanina, A.S.; Shergina, S.I.; Sokolov, I.E.; Kotlyarevskii, I.L. *Izvestiya Akademii Nauk USSR, Seriya Khimicheskayo.* **1981**, No. 5, 1158-1159; *Chem. Abstr.* **1981**, *95*, 97276s.
13. Ramachandran, P.V.; Teodorovic, A.V.; Rangaishenvi, M.V.; Brown, H.C. *J. Org. Chem.* **1992**, *57*, 2379-2386.
14. (a) Chowdhury, C.; Kundu, N.G. *J. Chem. Soc., Chem. Commun.* **1996**, 1067-1068; (b) Chaudhuri, G.; Chowdhury, C.; Kundu, N.G. *Synlett.* **1998**, 1273-1275; (c) Mahanty, J.S.; De. M.; Das, P.; Kundu, N.G. *Tetrahedron.* **1997**, *53*, 13397-13418.
15. Jones, E.R.H.; McCombie, J.T. *J. Chem. Soc.* **1942**, 733-735.
16. Kundu, N.G.; Schmitz, S.A. *J. Heterocyclic Chem.* **1982**, *19*, 463-464.
17. *Vogel's Text Book of Practical Organic Chemistry*, Longman Group Limited, London, 4th Edition, **1978**, p. 838.
18. (a) Fukue, Y.; Oi, S. and Inoue, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 2091; (b) Brandsma, L. *Preparative Acetylenic Chemistry*, Elsevier, Amsterdam, 1988.
19. (a) Kundu, N.G. ; Pal, M.; and Chowdhury, C. *J. Chem. Research* **1993**, 432-433. (b) Kundu, N.G.; Pal, M.; Mahanty, J.S.; De, M. *J. Chem. Soc.; Perkin Trans. 1.* **1997**, 2815-2820.