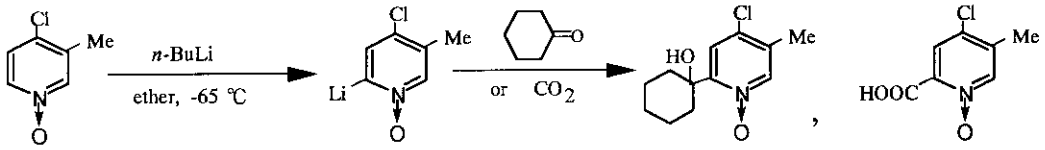
ELECTROPHILIC REACTION OF PYRIDINE, QUINOLINE, ISOQUINOLINE, THEIR *N*-OXIDES AND THEIR BORON TRIFLUORIDE COMPLEXES THROUGH BASE-INDUCED DEPROTONATION**

Yoshinobu Tagawa[a], Kazuya Hama[a], Yoshinobu Goto*[a], and Masatomo Hamana*[b]

a Faculty of Pharmaceutical Sciences, Fukuoka University, Nanakuma, Jonan-ku, Fukuoka 814-01, Japan
b Central Research Laboratories, Chugai Pharmaceutical Co. Ltd., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan

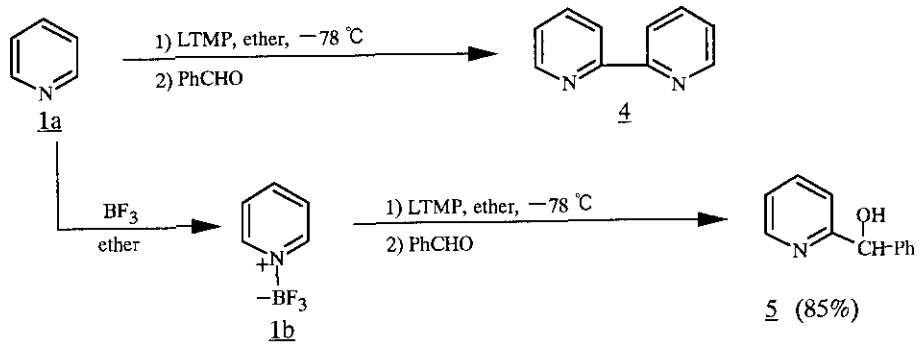
Abstract—The comparative studies have been carried out on reactivities of pyridine, quinoline, isoquinoline, and their BF_3 complexes, their *N*-oxides, and their *N*-oxide-BF_3 complexes, towards the electrophilic reaction through α-deprotonation.

Abramovitch and co-workers have reported on electrophilic substitutions of pyridine 1-oxides through α-lithiation by treatment with *n*-BuLi and electrophiles in ether at -65 °C as exemplified in Scheme 1.[1]
In 1991 Kessar *et al.* reported that a similar reaction occurred upon treatment boron trifluoride (BF_3) complex of pyridine (1b) with lithium 2,2,6,6-tetramethylpiperidide (LTMP) and an electrophile, e.g. benzaldehyde, in ether at -78 °C to provide the corresponding 2-substituted pyridine (5) in good yield, while 2,2'-bipyridine (4) was formed in the reaction of pyridine (1a) itself (Scheme 2).[2]



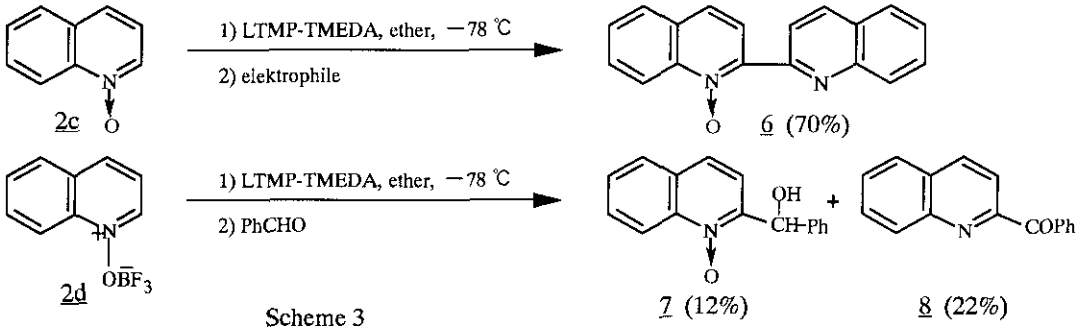
Scheme 1

**Dedicated to Professor Rolf Huisgen on the occasion of his 75th birthday.



Scheme 2

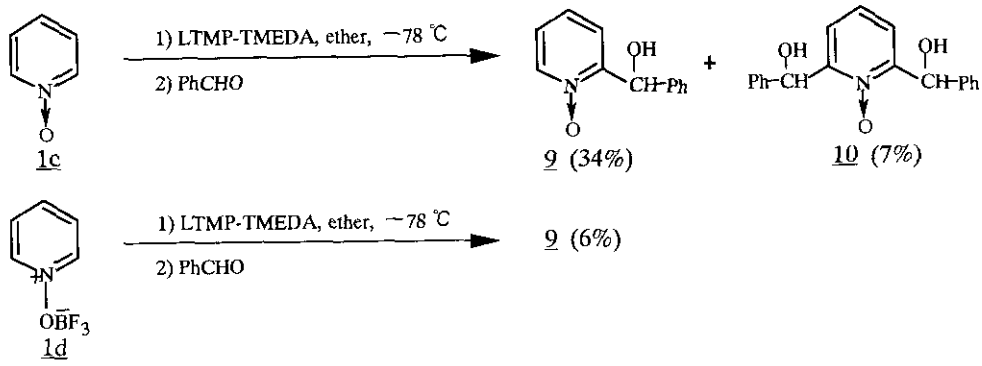
Recently we found that the reaction of quinoline 1-oxide-BF_3 complex (2d) with an electrophile, e.g. benzaldehyde, in the presence of LTMP and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) in ether at -78 °C [3] afforded 2-substituted products (7 and 8), but the reaction of quinoline 1-oxide (2c) under the same conditions resulted in the formation of 2,2'-biquinoline 1-oxide (6) (Scheme 3).[4]



Scheme 3

As a continuation of our studies on the electrophilic reaction of π-deficient *N*-heteroaromatics *via* α-deprotonation, we carried out the comparative studies on reactivities of pyridine (1a), quinoline (2a), isoquinoline (3a), and their BF_3 complexes (1b, 2b and 3b), their *N*-oxides (1c, 2c and 3c), and their *N*-oxide-BF_3 complexes (1d, 2d and 3d), towards the reaction with electrophiles in the presence of LTMP and TMEDA.

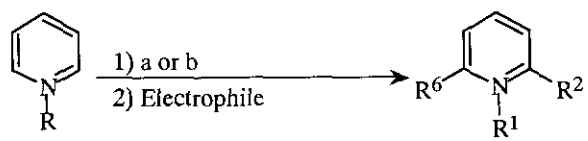
The reaction of pyridine 1-oxide (1c) with benzaldehyde was first examined in the presence of LTMP and TMEDA in ether at -78 °C and 2-(α-hydroxybenzyl)pyridine 1-oxide (9) and 2,6-di(α-hydroxybenzyl)pyridine 1-oxide (10) were obtained in 34 and 7% yields, respectively, accompanied by some recovery of 1c. On the other hand, the reactivity of pyridine 1-oxide-BF_3 complex (1d) under the same conditions was much lower and 9 was obtained in a very poor yield of 6% (Scheme 4).



Scheme 4

Similar results were obtained from reactions with acetophenone and benzophenone. Table I summarizes the results obtained hitherto in the pyridine series.

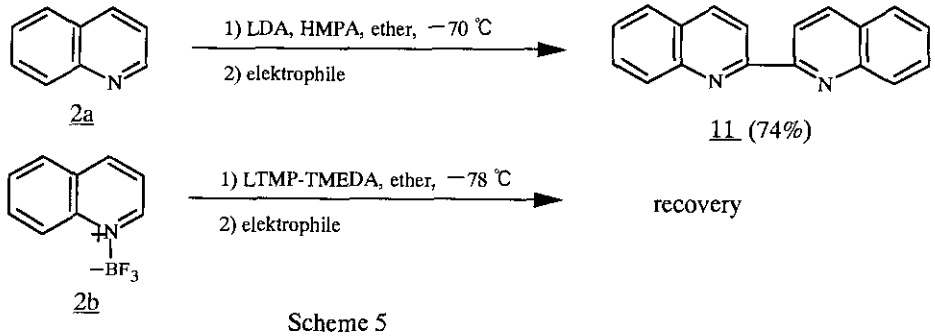
Table I. Reactions of Pyridine Series



				Product				
Substrate	*R*	*Conditions**	*Electrophile*	R^1	R^2	R^6	Yield, %**	(No.)**
1a	---	b	PhCHO	---	2-pyridyl	H	---[2]	(4)
1b	BF_3	b	PhCHO	---	CH(OH)Ph	H	85[2]	(5)
1c	O	a	PhCHO	O	CH(OH)Ph	H	34	(9)[6]
				O	CH(OH)Ph	CH(OH)Ph	7	(10)
1c	O	a	PhCOMe	O	C(OH)MePh	H	26	(14)[7]
				O	C(OH)MePh	C(OH)MePh	4	(15)
1c	O	a	PhCOPh	O	$C(OH)Ph_2$	H	24	(16)[8]
1d	OBF_3	a	PhCHO	O	CH(OH)Ph	H	6	(9)
1d	OBF_3	a	PhCOMe	O	C(OH)MePh	H	10	(14)
1d	OBF_3	a	PhCOPh	O	$C(OH)Ph_2$	H	3	(16)

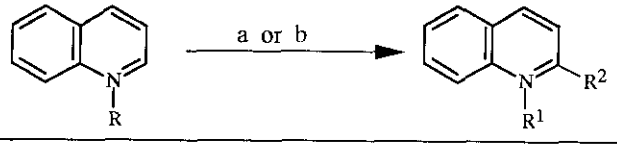
* a: LTMP, TMEDA, ether, -78 ℃ b: LTMP, ether, -78 ℃
** Superscript shows reference number.

Meth-Cohn *et al.* previously described that treatment of quinoline (2a) with an electrophile in the presence of lithium diisopropylamide (LDA) and hexamethylphosphoric triamide (HMPA) in ether at -70 °C gave 2,2'-biquinoline (11) in good yield.[5] We examined the reaction of quinoline-BF_3 complex (2b) with benzaldehyde in the presence of LTMP and TMEDA in ether at -78 °C and found that no reaction proceeded at all against our expectation, the starting material being quantitatively recovered (Scheme 5). Thus, the reactivities of the quinoline series may be summarized as Table II.



Scheme 5

Table II. Reactions of Quinoline Series

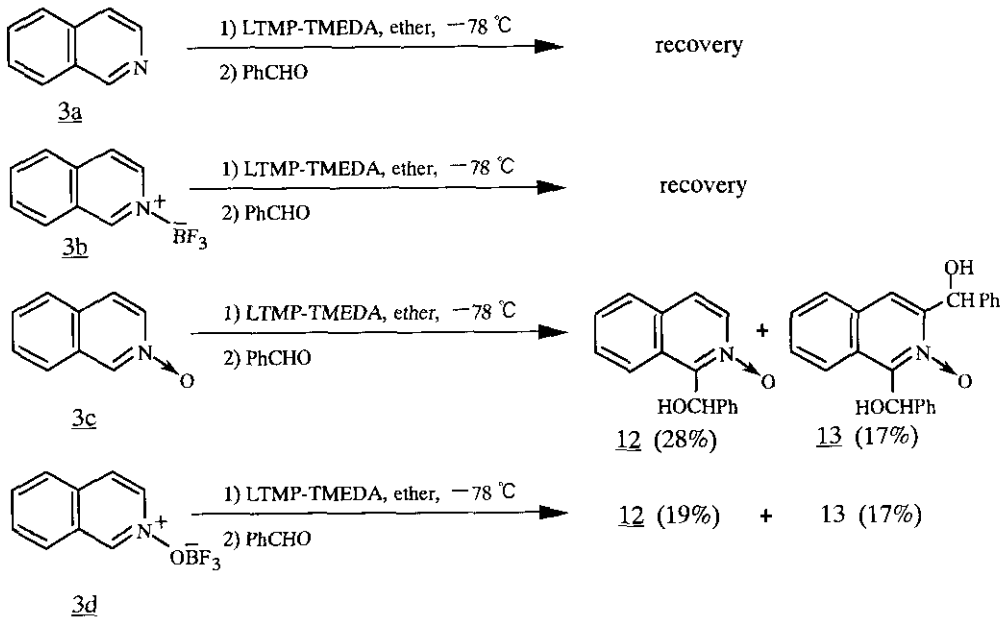


Substrate R		Conditions*	Product R^1	Product R^2	Yield, %**	(No.)
2a	---	a	---	2-quinolyl	74[5]	(11)
2b	BF_3	b	---	H	recovery	
2c	O	b	O	2-quinolyl	70	(6)
2d	OBF_3	b	O	CH(OH)Ph	12	(7)
			---	COPh	22	(8)

* a: 1) LDA-HMPA, ether, −70 °C, 2) electrophiles
b: 1) LTMP-TMEDA, ether, −78 °C, 2) PhCHO
** Superscript shows reference number.

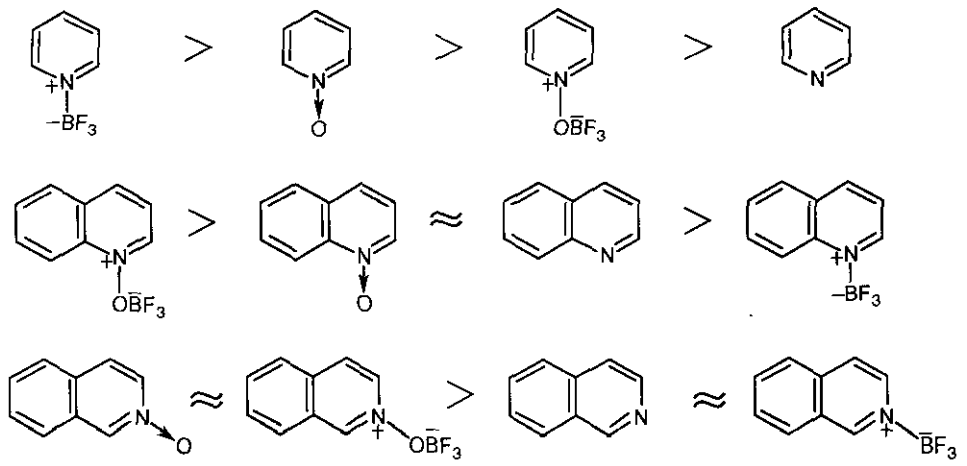
In the isoquinoline series, both isoquinoline 2-oxide (3c) and its BF_3 complex (3d) reacted with benzaldehyde under the same conditions to give the 1-substituted isoquinoline 2-oxide (12) and the 1,3-disubstituted isoquinoline 2-oxide (13); 3c seems to be somewhat more reactive than 3d. In this case the formation of 1,4-disubstituted isoquinoline 2-oxide could be also possible, but the possibility was ruled out by the comparison

of the C-H coupling constant[9] and chemical shift with other isoquinoline 2-oxides including 3-methylisoquinoline 2-oxide.[10] No reaction was noticed in the cases of isoquinoline (3a) and its BF_3 complex (3b) (Scheme 6).



Scheme 6

Thus it was disclosed that the reactivity order for the electrophilic reaction through α-deprotonation in each case is as follows (Scheme 7).



Scheme 7

EXPERIMENTAL

Melting points were measured on a Yanagimoto micro melting points apparatus and are uncorrected. Spectral data were recorded on the following spectrophotometers and spectrometers: infrared (IR) spectra, JASCO IR-810; ^{1}H-NMR spectra, JEOL GX-400 (400MHz); ^{13}C-NMR spectra JEOL GX-400 (100MHz); mass spectra (ms), JEOL JMS-DX300 for EI-ms and JMS-HX110 for FAB-ms. The yields of products were determined on a Shimadzu high speed thin layer chromatoscanner (CS-920) with the detector set at UV 254nm. Medium-pressure liquid chromatography was carried out with Yamazen 540 FMI-C pump and Kieselgel 60 (230-400mesh, Merck).

General procedure for electrophilic reaction of N-heteroaromatics and their BF_3 complex at -78 °C in the presence of LTMP-TMEDA-----LTMP-TMEDA solution was prepared by mixing of ether (10 ml), TMP (0.85 g, 6.0 mmol), 1.6M *n*-BuLi hexane solution (3.8 ml, 6.0 mmol) and TMEDA (0.70 g, 6.0 mmol) at 0 °C under nitrogen which was further stirred for 0.5 h at room temperature. To a solution of *N*-heteroaromatics or their BF_3 complex (5.0 mmol) in ether (30 ml), LTMP-TMEDA solution was added dropwise at -78 °C under nitrogen with stirring and after stirring for 2.5 h electrophile (6.0 mmol) was added to the reaction mixture which was further stirred for 1.5 h at -78 °C. The resulting reaction mixture was allowed to reach room temperature overnight with stirring and then the reaction was quenched with saturated ammonium chloride solution. The resulting solution was extracted with ether or dichloromethane and after removal of the solvent the residue was respectively post-treated in the manner as shown below.

Reaction of pyridine 1-oxide (1c) with benzaldehyde

The residue was purified by medium-pressure liquid chromatography (AcOEt) to afford 2-(α-hydroxybenzyl)pyridine 1-oxide (9) and 2,6-di(α-hydroxybenzyl)pyridine 1-oxide (10). Compound (9)was recrystallized from acetone to give pale yellow prisms, mp 170-171 °C (lit.,[6] 166-167 °C), 0.34 g (34% yield). Compound (10)was recrystallized from acetone to give colorless prisms, mp 181-182.5 °C, 0.11 g (7% yield). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25 ; H, 5.58 ; N, 4.56. Found: C, 74.15 ; H, 5.75 ; N, 4.59. Ir (KBr, cm^{-1}) : 3350, 1494, 1453, 1389, 1235, 1189, 1049, 919, 843, 743, 699. ^{1}H-Nmr (DMSO-d_6)δ : 6.08(2H, d, J=4.9 Hz, -CH-OH), 6.14(2H, d, J=4.4 Hz, -CH-OH), 7.20-7.31(6H, m, Ar-H), 7.37-7.40(4H, m, Ar-H), 7.48(1H, t, J=7.8 Hz, H-4), 7.67(2H, d, J=7.8 Hz, H-3 and H-5). ^{13}C-Nmr(DMSO-d_6)δ : 68.2(d, -CH-OH ×2), 121.65(d, Ar), 124.90(d, Ar), 127.04(d, Ar), 127.22(d, Ar), 127.86(d, Ar), 141.72(s, Ar), 153.56(s, Ar). EI-ms m/z (%) : 307(M^+, 12), 289(55), 272(100), 196(51), 183(42), 167(48), 105(64).

Reaction of pyridine 1-oxide BF_3 complex (1d) with benzaldehyde

The residue was purified by medium-pressure liquid chromatography (AcOEt) to give 9, 0.06 g(6% yield).

Reaction of 1c with benzophenone

The residue was purified by medium-pressure liquid chromatography (AcOEt) to give 2-(1-hydroxy-1,1-diphenylmethyl)pyridine 1-oxide (16). Compound (16)was recrystallized from acetone to give colorless needles, mp 202.5-203 °C (lit.,[8] 194 °C), 0.33 g (24% yield).

Reaction of 1d with benzophenone

The residue was purified by medium-pressure liquid chromatography (AcOEt) to give 16, 0.04 g (3% yield).

Reaction of 1c with acetophenone

The residue was purified by medium-pressure liquid chromatography (AcOEt) to give 2-(1-hydroxy-1-

methylbenzyl)pyridine 1-oxide (14) and 2,6-di(1-hydroxy-1-methylbenzyl)pyridine 1-oxide (15). Compound (14)was recrystallized from ether to give pale yellow needles, mp 117.5-118 °C (lit.,[7] 112-113 °C), 0.28 g (26% yield). Compound (15) was recrystallized from ether-acetone to give colorless needles, mp 191.5-192 °C, 0.07 g (4% yield). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found : C, 75.18; H, 6.33; N, 4.27. Ir(KBr, cm^{-1}) : 3418, 2992, 1342, 1218, 1176, 1041, 764, 698. ^{1}H-Nmr($CDCl_3$)δ : 1.89(6H, s, CH_3×2), 7.15-7.20(10H, m, Ar-H), 7.42-7.47(5H, m, Ar-H and OH×2). ^{13}C-Nmr($CDCl_3$)δ : 28.93(s, CH_3×2), 76.01(s, -C-OH×2), 123.31(d, Ar), 124.59(d, Ar), 127.06(d, Ar), 127.80(d, Ar), 128.08(d, Ar), 145.32(s, Ar), 154.96(s, Ar). FAB-ms m/z : 336$(M+H)^+$.

Reaction of 1d with acetophenone

The residue was purified by medium-pressure liquid chromatography (AcOEt) to give 14, 0.11 g (10% yield).

Reaction of isoquinoline 2-oxide (3c) with benzaldehyde

The residue was purified by medium-pressure liquid chromatography to give 1,3-di(α-hydroxybenzyl)isoquinoline 2-oxide (13) with the mixed solvent of n-hexane:AcOEt=5:1 as eluent and 1-(α-hydroxybenzyl)isoquinoline 2-oxide (12) with the mixed solvent of n-hexane:AcOEt=1:1 as eluent. Compound (12) was recrystallized from AcOEt to give colorless needles, mp 163 °C, 0.35 g (28% yield).

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.22; N, 5.57. Found : C, 76.36; H, 5.27; N, 5.85. Ir(KBr, cm^{-1}) : 3068, 1215, 1199, 1139, 815, 744, 707, 607. ^{1}H-Nmr($CDCl_3$)δ : 6.72(1H, d, J=10.3Hz, -CH-OH), 7.21-7.31(3H, m, Ar-H), 7.45(2H, d, J=7.8Hz, Ar-H), 7.61-7.71(3H, m, Ar-H), 7.82(1H, d, J=7.8Hz, Ar-H), 8.05(1H, d, J=7.3Hz, Ar-H), 8.13(2H, d, J=8.3Hz, Ar-H and OH). ^{13}C-Nmr($CDCl_3$)δ : 70.13(s, -CH-OH), 123.18(d, Ar), 123.56(d, Ar), 125.86(d, Ar), 127.58(d, Ar), 127.64(d, Ar), 127.70(s, Ar), 128.40(d, Ar), 129.28(d, Ar), 129.69(s, Ar), 129.87(d, Ar), 136.84(d, Ar), 140.52(s, Ar), 146.88(s, Ar). FAB-ms m/z : 252$(M+H)^+$.

Compound (13)was recrystallized from n-hexane-ether to give colorless prisms, mp 154-155 °C, 0.3 g (17% yield). Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found : C, 77.27; H, 5.48; N, 4.04. Ir(KBr, cm^{-1}) : 3342, 1493, 1452, 1195, 1145, 1059, 750, 698. ^{1}H-Nmr(DMSO-d_6)δ : 6.30(1H, d, J=4.9Hz, -CH-OH), 6.35(1H, d, J=4.9Hz, OH), 7.07(1H, d, J=6.4Hz, OH), 7.16-7.44(12H, m, Ar-H and -CH-OH), 7.55-7.61(2H, m, Ar-H), 8.03(1H, d, J=7.3Hz, Ar-H), 8.21(1H, s, Ar-H), 8.42(1H, d, J=8.3Hz, Ar-H). ^{13}C-Nmr(DMSO-d_6)δ : 67.22(s, -CH-OH), 68.86(s, -CH-OH), 120.75(d, Ar), 124.15(d, Ar), 125.06(d, Ar), 125.22(s, Ar), 126.14(d, Ar), 126.84(d, Ar), 126.93(d, Ar), 127.17(d, Ar), 127.31(d, Ar), 127.49(d, Ar), 127.89(d, Ar), 128.07(d, Ar), 128.13(d, Ar), 128.22(d, Ar), 128.39(d, Ar), 128.66(s, Ar), 142.13(s, Ar), 142.19(s, Ar), 148.43(s, Ar), 149.96(s, Ar). FAB-ms m/z : 358$(M+H)^+$.

Reaction of isoquinoline 2-oxide BF_3 complex (3d) with benzaldehyde

The residue was treated as similarly as in the reaction of 3c with benzaldehyde to give 12, 0.24 g (19% yield) and 13, 0.3 g (17% yield).

REFERENCES

1. a) R. A. Abramovitch, M. Saha, and R. T. Coutts, *J. Am. Chem. Soc.*, 1967, **89**, 1537; b) R. A. Abramovitch, E. M. Smith, E. E. Knaus, and M. Saha, *J. Org. Chem.*, 1972, **37**, 1690; c) R. A. Abramovitch, R. T. Coutts, and E. M. Smith, *ibid.*, 1972, **37**, 3584.

2. S. V. Kessar, P. Singh, K. N. Singh, and M. Dutt, *J. Chem. Soc., Chem. Commun.*, 1991, 570.
3. Y. Aoyagi, A. Maeda, M. Inoue, M. Shiraishi, Y. Sakakibara, Y. Fukui, and A. Ohta, *Heterocycles*, 1991, **32**, 735.
4. Y. Tagawa, K. Hama, Y. Goto, and M. Hamana, *Heterocycles*, 1992, **34**, 2243.
5. A. J. Clarke, S. McNamara, and O. Meth-Cohn, *Tetrahedron Lett.*, 1974, 2373.
6. C. W. Muth, J. C. Patton, B. Bhattacharya, D. L. Giberson, and C. A. Ferguson, *J. Heterocycl. Chem.*, 1972, **9**, 1299.
7. V. Boekelheide and W. L. Lehn, *J. Org. Chem.*, 1961, **26**, 428.
8. B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, 1951, **73**, 2196.
9. a) E. Breitmaier and W. Voelter "Carbon-13 NMR Spectroscopy", VCH, Weinheim, 1987, p.286 ; b) H. Günther and A. Gronenborn, *Heterocycles*, 1978, **11**, 337.
10. M. M. Robison and B. L. Robison, *J. Org. Chem.*, 1957, **21**, 1337.

Received, 6th June, 1994