A CONVENIENT SYNTHETIC METHOD FOR FLUORINE-CONTAINING BENZO[*h*]QUINOLINES FROM 2,4-BIS(TRIFLUOROACETYL)-1-NAPHTHYLAMINE AND KETONES

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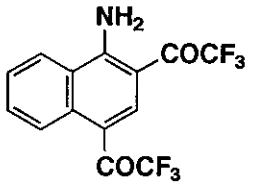
Abstract - 2,4-Bis(trifluoroacetyl)-1-naphthylamine (**1**) reacted easily with various ketones in the presence of aqueous ammonia or triethylamine to afford 6-trifluoroacetyl-4-trifluoromethylbenzo[*h*]quinolines (**2**) in moderate to excellent yields.

In recent years much attention has been paid to the development of new methodologies for the syntheses of many kinds of fluorine-containing heterocycles, since these compounds are now widely recognized as important organic materials showing interesting biological activities for their potential use in medicinal and agricultural scientific fields.[1] Previously, we reported that *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine undergoes a novel aromatic nucleophilic substitution with various amines, thiols, and alcohols to give the corresponding 2,4-bis(trifluoroacetyl)-1-naphthylamines, sulfides, and ethers in high yields.[2] Later, we succeeded in applying this type of aromatic nucleophilic substitution and the related reactions to the simple syntheses of various naphthalene-fused heterocycles bearing trifluoromethyl groups.[3] In connection with these works, we found recently that 2,4-bis(trifluoroacetyl)-1-naphthylamine (**1**) reacted with various aldehydes in the presence of aqueous ammonia to yield fluorine-containing benzo[*h*]quinazolines[4] and further discovered an efficient access to 3-substituted 6-trifluoroacetyl-4-

trifluoromethylbenzo[*h*]quinolines through the ring forming reaction between *N*-propargyl derivative of **1** and *N*-, *S*- and *O*-nucleophiles.[5] As a part of our systematic research program on the simple syntheses of CF_3-containing heterocycles, we now describe here the convenient synthesis of 2,3-disubstituted or 2-substituted 6-trifluoroacetyl-4-trifluoromethylbenzo[*h*]quinolines (**2**) by the reaction of **1** with various ketones in the presence of aqueous ammonia or triethylamine. These fluorine-containing benzoquinolines (**2**) are expected to show interesting pharmacological properties as antimicrobial agents and antitumor drugs.[6]

Reaction of **1**[2a] with acetone in the presence of aqueous ammonia proceeded easily under mild conditions to give 6-trifluoroacetyl-4-trifluoromethyl-2-methylbenzo[*h*]quinoline (**2a**) in 87% yield without being accompanied by the corresponding benzo[*h*]quinazoline (**3a**) of which the formation we expected originally on the basis of the reaction of **1** with aldehydes (Table 1).[4] 2,2-Diethyl-6-trifluoroacetyl-4-trifluoromethyl-1,2-dihydrobenzo[*h*]quinazoline (**3b**), however, was formed in 51% yield with 42% yield of benzo[*h*]-quinoline (**2b**) in the reaction with 3-pentanone. Separation of the **2b** - **3b** mixtures was easily effected



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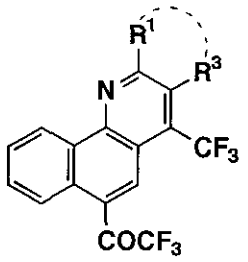

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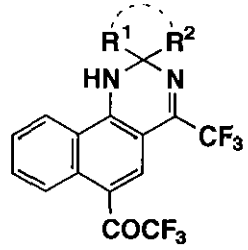

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Table 1. Reaction of **1** with Ketones (R^1COR^2) in the Presence of Aqueous Ammonia[a)]

Entry	R^1	R^2	R^3	$\frac{R^1COR^2}{\text{equiv.}}$	Temp (℃)	Time (h)	Product	Yield (%)
1	Me	Me	H	3	30	48	**2a**	87
2	Et	Et	Me	5	100[b)]	24	**2b/3b**	42/51
3	C_2H_4	C_2H_4	CH_2	1.2	rt	24	**2c**	90
4	C_3H_6	C_2H_4	CH_2	5	50	24	**2d/3d**	40/53
5	C_4H_8	C_2H_4	CH_2	2	50	24	**2e**	89
6	Et	Me	H	5	50	24	**2f/3f**	65/12[c)]
7	*i*-Pr	Me	H	5	50	48	**2g/3g**	84/6
8	Ph	Me	H	5	50	96	**2h**	92

a) Molar ratio, **[1]** / $[NH_3]$=1 / 1.2 ; MeCN was used as a solvent. b) In a sealed tube with PrCN as a solvent. c) With 13% yield of **2f'** (R^1=R^3=Me).

by chromatography. Next, we examined the reaction of **1** with cyclic ketones in order to synthesize benzo-[*h*]quinolines fused by cycloalkane rings. In the cases of cyclopentanone and cycloheptanone, the desired benzo[*h*]quinolines (**2c**,**e**) were exclusively obtained in high yields. However, **1** reacted with cyclohexanone to provide spiro type of benzoquinazoline (**3d**) predominantly. Further, the present reaction was applicable to some unsymmetrical ketones, such as 2-butanone and 3-methyl-2-butanone. In both cases, the desired benzoquinolines (**2f**,**g**) were obtained in 65-84% yields, together with small amounts of benzoquinazolines (**3f**,**g**). It is of interest that 13% yield of 2,3-dimethyl derivative (**2f'**) was generated in the reaction with 2-butanone. Quite similarly, reaction of **1** with acetophenone proceeded easily to give selectively 2-phenyl derivative of benzo[*h*]quinoline (**2h**) in 92% yield. For the sake of avoiding the formation of benzoquinazolines (**3b**,**d**,**f**,**g**), we tried to replace ammonia by triethylamine as a base in the present reaction (Table 2). Expectedly, in the reaction of **1** with 3-pentanone in the presence of

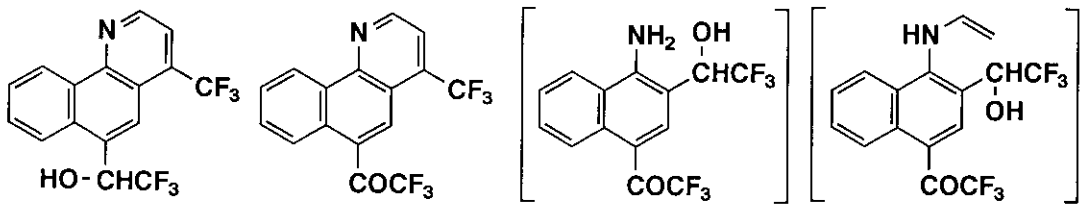
Table 2. Reaction of **1** with Ketones (R^1COR^2) in the Presence of Triethylamine[a)]

Entry	R^1	R^2	R^3	Temp (℃)	Time (d)	Product	Yield (%)
1	Et	Et	Me	50	14	**2b**	56[b)]
2	Et	Et	Me	60	10	**2b/4**	55/19
3	Et	Et	Me	82	5	**2b/4**	49/32
4	C_3H_6	C_2H_4	CH_2	50	10	**2d**	71
5	Et	Me	H	50	4	**2f**	60[c)]
6	*i*-Pr	Me	H	50	10	**2g**	67

a) Molar ratio, [**1**] / [R^1COR^2] / [Et_3N]=1 / 5 / 5 ; MeCN was used as a solvent. b) With 20% yield of Substrate **1**. c) With 14% yield of **2f'** (R^1=R^3=Me).

triethylamine at 50 ℃ for 14 d, the desired benzoquinoline (**2b**) was merely obtained in 56% yield without any formation of benzoquinazoline (**3b**) a nitrogen atom of which arose from ammonia as a base, although 20% of unreacted substrate (**1**) was recovered. Similarly, reactions with cyclohexanone, 2-butanone, and 3-methyl-2-butanone gave the desired benzoquinolines (**2d**,**f**,**g**) selectively in 60 - 71% yields. All reactions using triethylamine as a base required more forced reaction conditions than ammonia. Consequently aqueous ammonia is considered to be a better base-catalyst than triethylamine in the present synthetic method for benzo[*h*]quinolines (**2**). Next, we examined to carry out the reaction of **1** with 3-pentanone at higher temperature (60 and 82 ℃) for completing of the reaction, and the desired

benzoquinoline (**2b**) was obtained in 49 - 55% yields with no recovery of substrate (**1**). Interestingly, the unexpected 2,3-unsubstituted benzoquinoline (**4**) was newly formed in 19 - 32% yields. The yield of **4** gradually increased with elevating the reaction temperature. The reaction of **1** with triethylamine without 3-pentanone was undertaken for obtaining the information on the mechanism for the formation of **4**. The run at reflux temperature (90 ℃) for 48 h afforded **4** and **5**, considered as a **4**'s precursor, in 32% and 40% yields, respectively. Prolonged (5 d) heating resulted in yielding **4** as a sole product in 66% yield. A speculated reaction mechanism for the formation of **4** is as follows: reduction of **1** by triethylamine is thermally induced to provide amino alcohol (**6**) and *N*,*N*-diethylvinylamine. Nucleophilic attack of amino group of **6** to the olefinic carbon of *N*,*N*-diethylvinylamine and subsequent elimination of diethylamine take place to afford intermediary *N*-vinyl derivative (**7**). The formation of **5** is achieved by the ring closure accompanied by dehydration and dehydrogenation in **7**. Finally, trifluoroacetyl group of **5** is reduced again by triethylamine to yield alcohol (**4**). To the best of our knowledge, there have been no reports that triethylamine reduces carbonyl compounds.[7]



The structures of all new compounds (**2**-**5**) were determined on the basis of their ^{1}H-NMR and IR spectra, together with elemental analyses.

Thus, the present method provides a facile and convenient access to 2,3-disubstituted or 2-substituted 6-trifluoroacetyl-4-trifluoromethylbenzo[*h*]quinolines which are not easily obtained by other methods. Further utilization of **1** as a useful synthetic block for the preparation of various fluorine-containing naphthalene-fused heterocycles which are potentially medicinally active are now under investigation and will be presented elsewhere.

EXPERIMENTAL

All melting points were determined on an electrothermal digital melting point apparatus and are

uncorrected. IR spectra were recorded on a Hitachi EPI-G3 spectrophotometer. ^{1}H-NMR spectra were obtained with JEOL PMX 60SI instrument using $CDCl_3$ as a solvent unless otherwise indicated. All chemical shifts are reported in ppm downfield from internal tetramethylsilane; coupling constants (J) are given in Hz. Elemental analyses were performed by the Microanalyses Center of Kyoto University. Chromatographic separations were carried out on a silica gel column (Wakogel C-200; 100-200 mesh). All reagents were obtained commercially and used without further purification. Final purification of all products for elemental analyses was done by recrystallization.

Reaction of 2,4-Bis(trifluoroacetyl)-1-naphthylamine (1) with Ketones; General Procedure:

In the Presence of Ammonia : To a solution of **1**[2a] (335 mg, 1 mmol) in MeCN (5 mL) were added the appropriate ketone (1.2 - 5 mmol) and aqueous ammonia (28 wt.%, 73 mg, 1.2 mmol). The mixture was stirred at rt - 100 ℃ for 24 - 96 h, the solvent was removed under reduced pressure, and CH_2Cl_2 (50 mL) was added to the residue. This solution was washed with H_2O (100 mL) and dried (Na_2SO_4). The solvent was evaporated and the crude product was chromatographed using hexane/benzene (1:1) for **2a-h**, benzene/EtOAc (3:1) for **3b,g**, benzene/EtOAc (7:1) for **3f**, and hexane/benzene (1:3) for **3d** as eluent. The reaction of **1** with 3-pentanone was run in a sealed tube with PrCN as a solvent (see Table 1).

In the Presence of Triethylamine : To a solution of **1** (335 mg, 1 mmol) in MeCN (5 mL) were added the appropriate ketone (5 mmol) and triethylamine (506 mg, 5 mmol). The mixture was stirred at 50 - 82 (reflux) ℃ for 4 - 14 d. Following work-up and purification were carried out in a similar manner as above (see Table 2).

2a: mp 107-108 ℃ (hexane); IR (KBr) 1714, 1604, 1514 cm^{-1}; ^{1}H-NMR 9.35 (dd, 1H, J=3, 6, H-7), 8.77-8.40 (br, 2H, H-5, -10), 7.85-7.62 (m, 3H, H-3, -8, -9), 2.90 (s, 3H, CH_3). Anal. Calcd for $C_{17}H_9NOF_6$: C, 57.15; H, 2.54; N, 3.92. Found: C, 56.97; H, 2.46; N, 3.98.

2b: mp 148-149 ℃ (hexane); IR (KBr) 1712, 1580, 1510 cm^{-1}; ^{1}H-NMR 9.30 (dd, 1H, J=3, 6, H-7), 8.73-8.39 (m, 2H, H-5, -10), 7.80-7.52 (m, 2H, H-8, -9), 3.01 (q, 2H, J=7, C$\underline{H_2}$CH$_3$), 2.61 (q, 3H, J_{HF}=3, CH_3), 1.58 (q, 3H, J=6, $CH_2C\underline{H_3}$). Anal. Calcd for $C_{19}H_{13}NOF_6$: C, 59.23; H, 3.40; N, 3.64. Found: C, 59.30; H, 3.38; N, 3.60.

2c: mp 157-158 ℃ (hexane/$CHCl_3$); IR (KBr) 1713, 1602, 1575, 1517 cm^{-1}; ^{1}H-NMR 9.33-8.98 (m, 1H, H-7), 8.71-8.35 (m, 2H, H-5, -10), 7.81-7.44 (m, 2H, H-8, -9), 3.51-3.08 (m, 4H, CH_2), 2.48-

1.97 (m, 2H, CH_2). Anal. Calcd for $C_{19}H_{11}NOF_6$: C, 59.54; H, 2.89; N, 3.65. Found: C, 59.51; H, 2.84; N, 3.61.

2d: mp 111-112 ℃ (hexane/benzene); IR (KBr) 1706, 1602, 1572, 1510 cm^{-1}; ^{1}H-NMR 9.20 (dd, 1H, J=3, 6, H-7), 8.68-8.33 (m, 2H, H-5, -10), 8.05-7.60 (m, 2H, H-8, -9), 3.57-2.90 (br, 4H, CH_2), 2.20-1.80 (br m, 4H, CH_2). Anal. Calcd for $C_{20}H_{13}NOF_6$: C, 60.46; H, 3.30; N, 3.53. Found: C, 60.45; H, 3.19; N, 3.62.

2e: mp 132-133 ℃ (hexane); IR (KBr) 1717, 1599, 1575, 1511 cm^{-1}; ^{1}H-NMR 9.30-9.00 (m, 1H, H-7), 8.87 (br s, 1H, H-5), 8.59-8.31 (m, 1H, H-10), 7.70-7.41 (m, 2H, H-8, -9), 3.63-2.76 (br, 4H, CH_2), 1.86 (br s, 6H, CH_2). Anal. Calcd for $C_{21}H_{15}NOF_6$: C, 61.32; H, 3.68; N, 3.41. Found: C, 61.43; H, 3.62; N, 3.46.

2f: mp 106-107 ℃ (hexane); IR (KBr) 1714, 1605, 1514 cm^{-1}; ^{1}H-NMR 9.45-9.14 (m, 1H, H-7), 8.73-8.35 (m, 2H, H-5, -10), 7.80-7.50 (m, 3H, H-3, -8, -9), 3.15 (q, 2H, J=7, CH_2), 1.52 (t, 3H, J=7, CH_3). Anal. Calcd for $C_{18}H_{11}NOF_6$: C, 58.23; H, 2.99; N, 3.77. Found: C, 58.33; H, 2.71; N, 3.68.

2f': mp 119-120 ℃ (hexane); IR (KBr) 1709, 1602, 1585, 1514 cm^{-1}; ^{1}H-NMR 9.41-9.03 (m, 1H, H-7), 8.67-8.35 (m, 2H, H-5, -10), 7.80-7.47 (m, 2H, H-8, -9), 2.80 (s, 3H, CH_3-2), 2.57 (q, 3H, J_{HF}=3, CH_3-3). Anal. Calcd for $C_{18}H_{11}NOF_6$: C, 58.23; H, 2.99; N, 3.77. Found: C, 57.99; H, 3.16; N, 3.87.

2g: mp 100-101 ℃ (hexane/benzene); IR (KBr) 1717, 1604, 1565, 1511 cm^{-1}; ^{1}H-NMR 9.45-9.29 (m, 1H, H-7), 8.62-8.41 (m, 2H, H-5, -10), 7.81-7.52 (m, 3H, H-3, -8, -9), 3.45 (heptuplet, 1H, J=7, CH), 1.51 (d, 6H, J=7, CH_3). Anal. Calcd for $C_{19}H_{13}NOF_6$: C, 59.23; H, 3.40; N, 3.64. Found: C, 59.36; H, 3.28; N, 3.63.

2h: mp 148-149 ℃ (hexane); IR (KBr) 1715, 1595, 1558, 1509 cm^{-1}; ^{1}H-NMR 9.36-9.19 (m, 1H, H-7), 8.63-8.40 (m, 2H, H-5, -10), 8.19-8.03 (m, 3H, H-3, C_6H_5), 7.78-7.33 (m, 5H, H-8, -9, C_6H_5). Anal. Calcd for $C_{22}H_{11}NOF_6$: C, 63.02; H, 2.64; N, 3.34. Found: C, 62.75; H, 2.50; N, 3.63.

3b: mp 130-131 ℃ (hexane/CH_2Cl_2); IR (KBr) 3385, 3350, 1646, 1618, 1595, 1511 cm^{-1}; ^{1}H-NMR 9.30-9.14 (dd, 1H, J=2, 4, H-7), 8.35 (br s, 1H, H-5), 7.97-7.50 (m, 3H, H-8, -9, -10), 5.43 (br s, 1H, NH), 2.27-1.50 (m, 4H, $C\underline{H_2}CH_3$), 1.01 (t, 6H, J=7, $CH_2C\underline{H_3}$). Anal. Calcd for $C_{19}H_{16}N_2F_6O$: C, 56.72; H, 4.01; N, 6.96. Found: C, 56.70; H, 3.97; N, 7.02.

3d: mp 167-168 ℃ (hexane/$CHCl_3$); IR (KBr) 3425, 1655, 1615, 1597, 1565, 1515 cm^{-1}; ^{1}H-NMR

9.23-8.90 (dd, 1H, J=2, 4, H-7), 8.27 (br s, 1H, H-5), 7.93-7.13 (m, 3H, H-8, -9, -10), 5.63 (br s, 1H, NH), 2.50-0.90 (br, 10H, CH_2). Anal. Calcd for $C_{20}H_{16}N_2OF_6$: C, 57.97; H, 3.89; N, 6.76. Found: C, 57.69; H, 4.09; N, 6.82.

3f: mp 125-126 ℃ (hexane/$CHCl_3$); IR (KBr) 3342, 1639, 1618, 1584, 1529, 1512 cm^{-1}; ^{1}H-NMR 9.20-8.87 (m, 1H, H-7), 8.23 (br s, 1H, H-5), 7.93-7.30 (m, 3H, H-8, -9, -10), 5.50-5.20 (br, 1H, NH), 2.21-1.63 (m, 5H, $C\underline{H}_2CH_3$, CH_3), 1.00 (t, 3H, J=7, $CH_2C\underline{H}_3$). Anal. Calcd for $C_{18}H_{14}N_2OF_6$: C, 55.68; H, 3.63; N, 7.21. Found: C, 56.06; H, 3.56; N, 6.90.

3g: mp 129-130 ℃ (hexane/$CHCl_3$); IR (KBr) 3443, 1675, 1654, 1618, 1599, 1566, 1517 cm^{-1}; ^{1}H-NMR 9.27-9.03 (m, 1H, H-7), 8.35 (br s, 1H, H-5), 8.00-7.37 (m, 3H, H-8, -9, -10), 5.50 (br s, 1H, NH), 2.12 (heptuplet, 1H, J=7, $C\underline{H}(CH_3)_2$), 1.61 (s, 3H, CH_3), 1.08 (d, 6H, J=7, $CH(C\underline{H}_3)_2$). Anal. Calcd for $C_{19}H_{16}N_2OF_6$: C, 56.72; H, 4.01; N, 6.96. Found: C, 56.65; H, 4.01; N, 6.95.

Reaction of 1 with Triethylamine: A solution of **1** (335 mg, 1 mmol) in Et_3N (3.4 mL, 24.4 mmol) was refluxed with stirring for 48 h. Evaporation and subsequent chromatography using hexane/EtOAc (9/1) as an eluent gave **4** (110 mg, 32%) and **5** (137 mg, 40%).

4: mp 130-131 ℃ (hexane/$CHCl_3$); IR (KBr) 3300, 1593 cm^{-1}; ^{1}H-NMR 9.11 (dd, 1H, J=3,6, H-7), 8.92 (d, 1H, J=5, H-2), 8.25-7.42 (m, 5H, H-3, -5, -8, -9, -10), 5.84 (q, 1H, J_{HF}=7, $CHCF_3$), 5.32-4.30 (br, 1H, OH). Anal. Calcd for $C_{16}H_9NOF_6$: C, 55.66; H, 2.63; N, 4.06. Found: C, 55.41; H, 2.92; N, 4.02.

5: mp 134-135 ℃ (hexane/EtOAc); IR (KBr) 1708, 1598, 1522 cm^{-1}; ^{1}H-NMR 9.33 (dd, 1H, J=3, 6, H-7), 9.16 (d, 1H, J=5, H-2), 8.75-8.40 (m, 2H, H-5, -10), 7.91-7.63 (m, 3H, H-3, -8, -9). Anal. Calcd for $C_{16}H_7NOF_6$: C, 55.99; H, 2.06; N, 4.08. Found: C, 55.73; H, 2.31; N, 4.39.

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REFERENCES

1. a) R. Filler, 'Organofluorine Chemicals and Their Industrial Applications,' ed. by R. E. Banks, Ellis Horwood, London, 1979; b) R. Filler and Y. Kobayashi, 'Biomedicinal Aspects of Fluorine

Chemistry, 'Kodansha & Elsevier Biomedical, Tokyo, 1982; c) J. T. Welch, *Tetrahedron*, 1987, **43**, 3123; d) R. Filler, Y. Kobayashi, and L. M. Yagupolskii, 'Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications,' , Elsevier, Amsterdam, 1993.

2. a) M. Hojo, R. Masuda, and E. Okada, *Tetrahedron Lett.*, 1987, **28**, 6199; b) M. Hojo, R. Masuda, E. Okada, and H. Miya, *Synthesis*, 1989, 870; c) M. Hojo, R. Masuda, E. Okada, and H. Miya, *Chem. Express*, 1990, **5**, 485; d) M. Hojo, R. Masuda, E. Okada, and H. Miya, *Chem. Express*, 1990, **5**, 569.
3. a) M. Hojo, R. Masuda, E. Okada, and H. Miya, *Synthesis*, 1989, 550; b) E. Okada, R. Masuda, M. Hojo, N. Imazaki, and H. Miya, *Heterocycles* ,1992, **34**, 103; c) M. Hojo, R. Masuda, E. Okada, T. Tomifuji, and N. Imazaki, *Synthesis*, 1990, 1135; d) E. Okada, R. Masuda, M. Hojo, N. Imazaki, and K. Takahashi, *Synthesis*, 1992, 536; e) M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1990, 481; f) M. Hojo, R. Masuda, and E. Okada, *Tetrahedron Lett.*, 1988, **29**, 4599; g) E. Okada, R. Masuda, M. Hojo, and T. Tomifuji, *Heterocycles*, 1993, **36**, 845; h) E. Okada, R. Masuda, M. Hojo, H. Tone, and T. Tomifuji, *Heterocycles*, 1994, **37**, 157.
4. E. Okada, R. Masuda, M. Hojo, H. Tone, N. Gotoh, and T. Huang, *Heterocycles*, 1995, **40**, 905.
5. E. Okada, H. Tone, N. Tsukushi, Y. Otsuki, H. Takeuchi, and M. Hojo, *Heterocycles*, 1997, **45**, 339.
6. a) R. P. Bahuguna, Y. C. Joshi, M. P. Dobhal, B. C. Joshi, and H. N. Mangal, *Heterocycles*, 1981, **16**, 1955; b) R. P. Bahuguna and B. C. Joshi, *Indian J. Heterocycl. Chem.*, 1994, **3**, 265; c) R. P. Bahuguna and B. C. Joshi, *Egypt. J. Chem.*, 1988, **31**, 89; d) W. A. Denny, G. J. Atwell, and B. C. Baguley, *Anti-Cancer Drug Des.*, 1987, **2**, 263; e) G. Jones, ' Quinolines, ' ed. by G. Jones, Wiley-Interscience, London, 1977.
7. It has been reported that reduction of ketones and acyl chlorides using reducing agents such as sodium borohydride and zinc borohydride is catalyzed by triethylamine, see: a) H. C. Brown, E. J. Mead, and B. C. S. Rao, *J. Am. Chem. Soc.*, 1955, **77**, 6209; b) H. Kotsuki, Y. Ushio, N. Yoshimura, and M. Ochi, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 2684.

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