N-Bromosuccinimide Reactions of Some Heterocycles in the Presence or Absence of Water: An Overview of Ring Versus Side Chain Bromination for the Synthesis of Important Brominated Heterocyclic Synthons

Shyamaprosad Goswami*, Kumaresh Ghosh, Reshmi Mukherjee,
Avijit Kumar Adak and Ajit Kumar Mahapatra

Department of Chemistry, Bengal Engineering College (Deemed University), Howrah-711103, India
Received December 23, 1998

Dedicated to the Late Dr. Raymond N. Castle

Reactions of various heterocycles **1-6** with *N*-bromosuccinimide in the presence or absence of water have been studied for side chain versus ring bromination to afford some new and important heterocyclic synthons. Interestingly, the *N*-bromosuccinimide reaction in the presence of perchloric acid, a new condition, affords exclusively the new dibromo aminopicoline **1f**, which is not obtained by other presently studied methods.

J. Heterocyclic Chem., **38**, 173 (2001).

Specific functionalised heterocycles are highly desirable because of their many uses in heterocyclic chemistry, industrial chemistry and as ligands for neutral organic molecules [1]. Specifically, pyridine derivatives are important as precursors for pharmacologically active compounds [2], and for the synthesis of liquid crystals [3] and polymers *etc*.

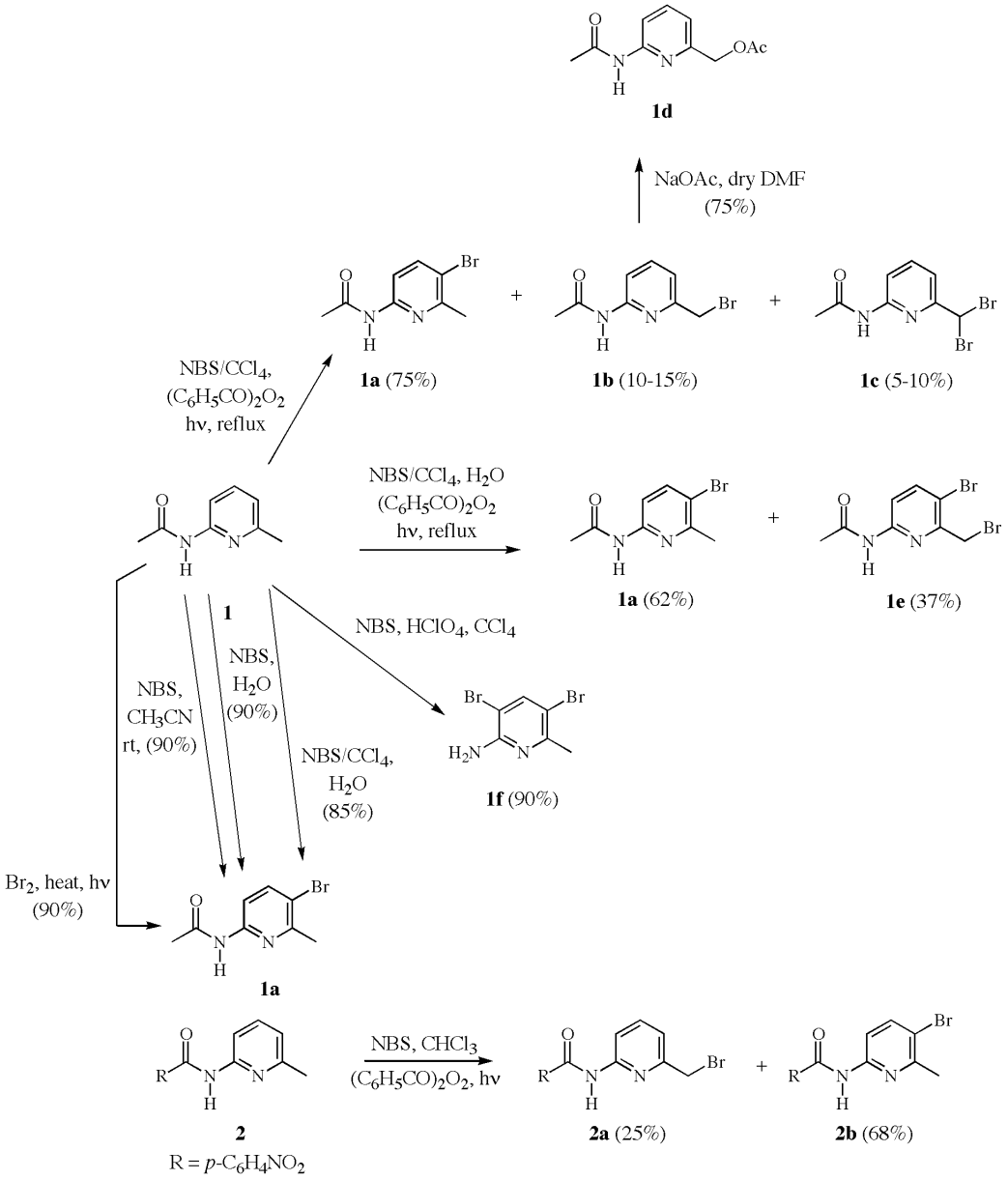
Bromination using *N*-bromosuccinimide, in the presence or absence of water, as well as with molecular bromine are undertaken on the pyridine and naphthyridine derivatives enroute to the synthesis of functionalised bromomethylpyridine or naphthyridine for our molecular recognition research [4a-d]. They are also prepared for the synthesis of heterocyclic benzylic bromides to study our newly discovered cobalt (I) oxidation reaction [4e].

N-bromosuccinimide reactions under different conditions [5] (*N*-bromosuccinimide in sodium hydroxide, in aqueous sulphuric acid or catalytic amount of concentrated sulphuric acid, *p*-toluenesulphonic acid, silica gel *etc*.) continue to be an area of active interest. From the known brominating agents for aromatic rings [6], *N*-bromosuccinimide is widely used in free radical, allylic or benzylic brominations [7] and also for the electrophilic substitution of aromatic rings [8]. Very recently, bromine in water [9] has been used for the free radical bromination of some selected nonheterocyclic compounds. We report here our results on acyl group protected 2-amino-6-methylpyridine, 2,6-dimethylpyridine and 2,7-dimethylpyridine under different conditions that generated some new, as well as known important ring or side chain brominated heterocyclic synthons. These were successfully characterised after, in some cases, a difficult separation (Schemes 1 and 2). By this method, a new convenient synthesis of 2-amino-6-pyridinemethanol has been developed from 2-phthalimido-6-bromomethylpyridine (Scheme 3).

The free radical side chain bromination of acetyl protected 2-amino-6-methylpyridine **1** with *N*-bromosuccinimide competes with the reaction leading to ring bromination. Bromination using molecular bromine on 2-amino-6-methylpyridine is reported [10] to afford ring bromo compounds. Treatment of 2-amino-4,6-lutidine with bromine in acetic acid or with *N*-bromosuccinimide in chloroform yields [11] only the 3,5-dibromo derivative resulting from ring bromination. The results of our investigation on the bromination of acetyl protected **1** and *p*-nitrobenzoyl protected (more electron withdrawing) 2-amino-6-methylpyridine **2** under different conditions are shown in Scheme 1.

The reaction of compound **1** with *N*-bromosuccinimide in dry carbon tetrachloride with a catalytic amount of benzoyl peroxide (3 mol%) gives the ring bromo derivative **1a** in 75% yield, the side chain monobromo derivative **1b** in 10-15% yield and also the dibromo derivative **1c** in 5-10% yield. Use of a large amount of carbon tetrachloride solvent slightly increases the yield of **1b**. Compound **1a** and **1b** have indentical R_f values and are therefore inseparable. As a result, compounds **1a** and **1b** were treated with sodium acetate and the resulting 2-*N*-acetamido-6-acetoxymethylpyridine (**1d**) was separated and characterised as the acetate derivative of **1b**. Presence of water droplets (about 10-15 equivalents) in this reaction condition accelerates the rate of *N*-bromosuccinimide reactions. Interestingly in the presence of water and benzoyl peroxide (3 mol%), **1a** is produced in 62% yield along with **1e**, a new bromo derivative in 37% yield. Under the same reaction conditions without the addition of benzoyl peroxide (i.e, *N*-bromosuccinimide in carbon tetrachloride, water, hν) only **1a** is produced within 1.5 hours in 85% yield. In the presence of benzoyl peroxide (3%) in pure water (as solvent) instead of carbon tetrachloride, **1a** is produced in 90% yield within 1 hour. Interestingly, there is no bromination reaction of 2,6-lutidine with *N*-bromosuccinimide in acetonitrile in the presence of light, without the presence of benzoyl peroxide or water at room temperature, however with refluxing the 6-bromomethyl-2-methylpyridine is obtained as the major product (50%) along with starting material. The effect of water in bromination reactions on heterocyclic compounds was further examined by starting with other heterocycles

Scheme 1

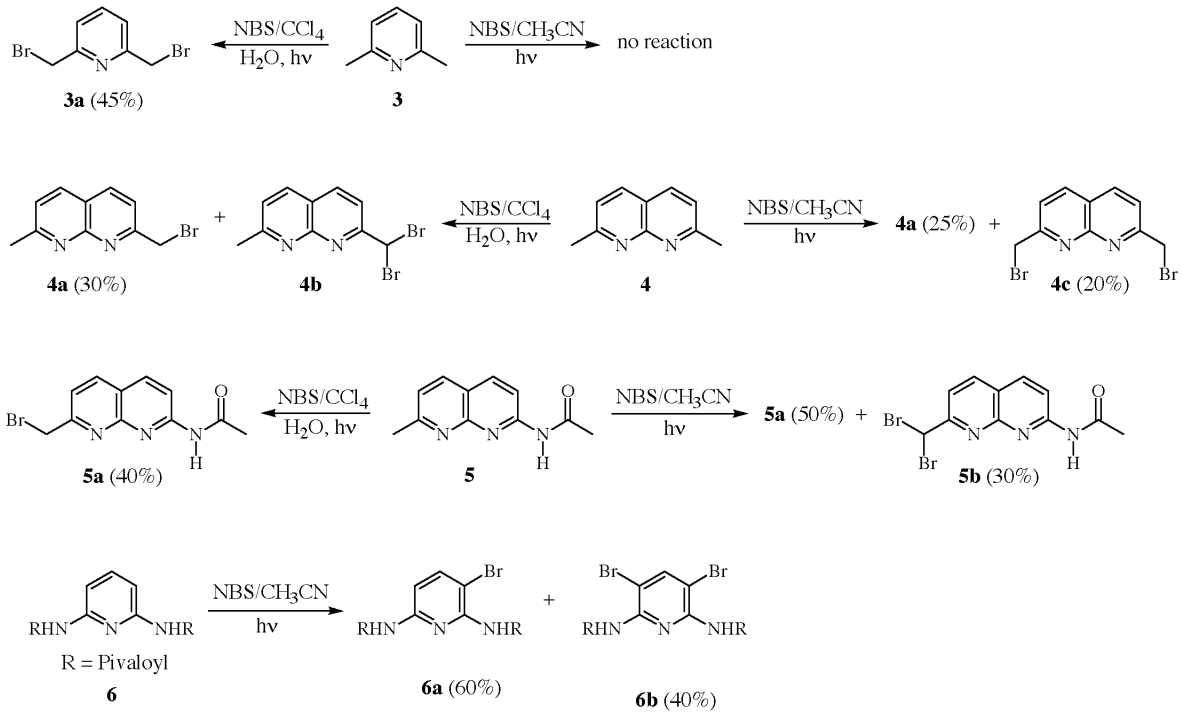


such as compounds **3**, **4** and **5** (Scheme 2). Bromination of **3** (*N*-bromosuccinimide in benzene) is reported to produce **3a** only in 20% yield [5], however using our procedure (*N*-bromosuccinimide along with benzoyl peroxide in dry carbon tetrachloride containing 15 equivalents of water), the yield of **3a** is enhanced to 45%.

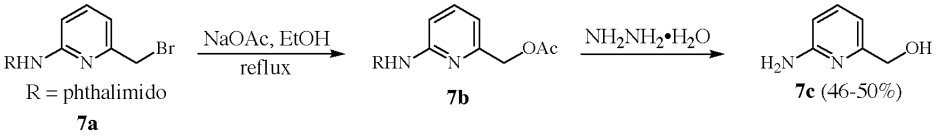
Compound **4** [12], in the presence of water, gives **4a** in 30% yield along with some of the dibromo product **4b**. The presence of water in this reaction marginally changes the yield of **4a** but makes the reaction faster. Under the same reaction condition, compound **5** gives **5a** in 40% yield while the previous reported condition of *N*-bromosuccinimide in chloroform gives 26% yield [12]. The bromination reaction of **4** with *N*-bromosuccinimide in acetonitrile in the presence of light without the addition of benzoyl peroxide or water afforded **4a** (25%) and the 2,6-dibromomethylnaphthyridine (**4c**) (20%) but **4b** was not obtained. Under the same reaction conditions, compound **5** affords compounds **5a** and **5b** in 50% and 30% respectively (Scheme 2). Interestingly, by treating 2,6-dipivaloylaminopyridine (**6**) with *N*-bromosuccinimide in acetonitrile in the presence of light without the presence of benzoyl peroxide or water products **6a** and **6b** are obtained in 60% and 40% respectively.

Thus, in most cases, the presence of water droplets in the bromination reaction accelerates the rate of bromination of heterocyclic compounds. The presence of water droplets

Scheme 2



Scheme 3



may increase the polarity of the solvent mixture and also the co-product hydrobromic acid, generated in the reaction medium, is scavenged and thus maintaining a more uniform distribution of free radicals thereby increasing the extent of side chain bromination relative to that of ring bromination. However, this effect varies depending on the substrate. Use of AIBN rather than benzoyl peroxide as radical initiator in the reaction medium also produces a similar effect.

In order to reduce the electron density in the pyridine ring, a factor responsible for ring bromination, the acetyl group in **1** is replaced by the more electron withdrawing 4-nitrobenzoyl group (Scheme 1). By changing to the more electronegative 4-nitrobenzoyl protecting group (compound **2**) from that of the acetyl group (compound **1**), the yield of side chain brominated product is found to increase to some extent (**2a**; 25%). This shows that by changing the protecting groups one can change the ratio of side chain (benzylic position) versus ring bromination. Use of perchloric acid to make a salt of **1** was then exploited to decrease the ring electron density, and it was hoped that it would reduce the ring brominated product. However, compound **1** in the presence of perchloric acid in carbon tetrachloride produces another interesting new product (**1f**, 90%) where the protecting acetyl group is simultaneously deprotected. The new dibromo product **1f**, which is potentially useful for the synthesis of polyaza heterocycles, cannot be obtained by other combinations that we have used here. The presence of perchloric acid in bromination of **2** gives **2a** (without deprotecting the 4-nitrobenzoyl group) instead of **1f** without significant improvement of the yield. The absence of **1f** from **2**, under this condition of the *N*-bromosuccinimide reaction, likely results because the 4-nitrobenzoyl group remains intact in this case. All these perchloric acid mediated bromination reactions in the absence of benzoylperoxide show the same effect, although the mechanistic role of benzoylperoxide is still not clear to us.

N-bromosuccinimide in acetonitrile, a mild and regiospecific nuclear brominating agent [8], gives **1a** as the sole product from **1** (Scheme 1). This combination of

Table 1

Starting material	Product	Yield (%)	mp (°C)	^{1}H NMR (deuteriochloroform) and mass (M^+) of major compounds
1	**1a**	75 [a] 62 [b] 90 [c] 85 [d] 90 [e]	155	7.91 (d, 1H, J = 8 Hz), 7.88 (s, 1H), 7.75 (d, 1H, J = 8 Hz), 2.53 (s, 3H), 2.19 (s, 3H); M^+: 228, 230
1	**1b** [f]	10-15 [a]	-	8.13 (d, 1H, J = 8 Hz), 7.92 (s, -NH-), 7.70 (t, 1H, J = 8 Hz), 7.14 (d, 1H, J = 8 Hz), 4.41 (s, 2H), 2.21 (s, 3H);
	1c [f,g]	5-10 [a]	-	8.15 (d, 1H, J = 8 Hz), 7.96 (s, NH), 7.75 (t, 1H, J = 8 Hz), 7.36 (d, 1H, J = 8 Hz), 6.50 (s, 1H), 2.20 (s, 3H);
1	**1e**	37 [b]	198-200	8.05 (d, 1H, J = 8 Hz), 7.84 (s, -NH-), 7.82 (d, 1H, J = 8 Hz), 4.55 (s, 2H), 2.21 (s, 3H). M^+: 308, 310.
1	**1f**	90	134	7.72 (s, 1H), 4.84 (bs, NH_2), 2.44 (s, 3H).
2	**2a**	25 [a]	107-109	8.62 (s, NH), 8.38 (d, 2H, J = 10 Hz), 8.31 (d, 1H, J = 8Hz), 8.13 (d, 2H, J = 10 Hz), 7.80 (t, 1H, J = 8 Hz), 7.23 (d, 1H, J = 8 Hz), 4.44 (s, 2H). M^+: 336, 338.
2	**2b**	68 [a]	192-194	8.45 (s, NH), 8.36 (d, 2H, J = 8 Hz), 8.09 (d, 3H, J = 8Hz), 7.85 (d, 1H J = 8 Hz), 2.58 (s, 3H).
3	**3a** [g]	45 [b]	82	7.70 (t, 1H, J = 8 Hz), 7.35 (d, 2H, J = 8 Hz), 4.53 (s, 4H).
	3b		-	
4	**4a**	26 [a] 30 [b]	128-130[h]	8.20 (d, 1H, J = 8 Hz), 8.06 (d, 1H, J = 8 Hz), 7.63 (d, 1H, J = 8 Hz), 7.43 (d, 1H, J = 8 Hz), 4.74 (s, 2H), 2.89 (s, 3H). M^+: 236, 238.
4	**4b** [f]		-	8.29 (d, 1H, J = 8 Hz), 8.23 (d, 1H, J = 8 Hz), 7.70 (d, 1H, J = 8 Hz), 7.45 (d, 1H, J = 8 Hz), 4.74 (s, 2H), 6.85 (s, 1H).
	4c	20	239 (dec.)	8.22 (d, 2H, J = 8.26), 7.72 (d, 2H, J = 8.2), 4.76 (s, 4H).
5	**5a** [g]	40 [b]	-	
	5b		169	8.57 (1H, d, J = 8.82), 8.38 (bs, 1H), 8.27 (1H, d, J = 8.40), 8.22 (1H, d, J = 8.82), 8.05(1H, d, J = 7.84), 6.77 (1H, s), 2.3 (3H, s).
6	**6a**	60 [c]	80	8.73 (s, 1H), 8.15 (s, 1H), 7.49 (d, 1H, J = 8Hz), 7.80 (d, 1H, J = 8 Hz), 1.35 (s, 9H), 1.25 (s, 9H).
6	**6b**	40 [c]	228	8.15 (s, 2H), 8.04 (s, 1H), 1.34 (s, 18H).
7	**7a**	62 [b]	125-130	8.16 (m, 3H), 7.81 (m, 2H), 7.54 (d, 1H, J = 8Hz), 7.35 (d, 1H, J = 8 Hz), 4.59 (s, 2H).
7	**7c**	46-50	93	7.27 (t, 1H, J = 8 Hz), 6.42 (d, 1H, J = 8 Hz), 6.30 (d, 1H, J = 8Hz), 5.5 (brs, 1H, -OH), 4.44 (s, 2H), 3.5 (brs, 2H, -NH_2).

[a] *N*-bromosuccinimide in the absence of water in carbon tetrachloride; [b] *N*-bromosuccinimide in the presence of water in carbon tetrachloride; [c] *N*-bromosuccinimide in acetonitrile; [d] *N*-bromosuccinimide in the absence of benzoyl peroxide in carbon tetrachloride containing water; [e] *N*-bromosuccinimide in pure water; [f] characterised from the mixture due to difficulty in purification; [g] characterised by comparison of NMR and mp data with literature; [h] decomposition temperature.

N-bromosuccinimide/acetonitrile affords the ring brominated products (**6a** and **6b**) from 2,6-dipivaloylaminopyridine **6** in better yields compared to the method of bromine in acetic acid (Scheme 2). Therefore, side-chain bromination over ring bromination of 2-amino-6-methylpyridine was really an interesting problem for 2-amino-6-methylpyridine until the phthalimido protected amino picoline **7** [13] was chosen, where the resonating lone pair of amino nitrogen towards pyridine ring is locked, that affords a good yield of benzylic bromination without any ring bromination product. In this case, the presence of water did not significantly change the yield of the side chain monobromination product **7a** from 2-*N*-phthalimido-6-methylpyridine. This phthalimido monobromo product **7a** is important as it was conveniently converted to **7c** *via* the intermediacy of the uncharacterised **7b** (Scheme 3). To our knowledge, the single step deprotection of both phthalimido as well as acetate groups of **7b** represents a new route for the synthesis of 2-amino-6-methylpyridine **7c** [14]. The physical constants and spectral details of new compounds are given in Table 1.

In summary, we have studied the *N*-bromosuccinimide reactions of various heterocycles in the presence and in the absence of water, in some cases giving an overview of side-chain versus ring bromination. The cases where side-chain bromination is favoured over ring bromination may be the result of a change in the polarity of the solvent mixture due to the addition of water. This is the first report of *N*-bromosuccinimide reactions of heterocycles in water. Interestingly, the *N*-bromosuccinimide reaction, in the presence of perchloric acid, afford exclusively the new

dibromo aminopicoline **1f**, which is not obtained by other presently studied methods. The details of the mechanism and the applications of this reaction in different conditions with heterocycles are however not completed and further work is in progress. This will be reported in due course.

EXPERIMENTAL

All reactions are carried out under nitrogen. Compounds were purified by repeated silica gel (60-120 mesh) chromatography as well as preparative tlc. For bromination, a 250 W ordinary bulb was used as a light source.

General Procedure for *N*-Bromosuccinimide Reaction.

In the Absence of Water.

A stirred mixture of 2-acetamido-6-methylpyridine (1g, 6.6 mmol), *N*-bromosuccinimide (1.42 g, 8.0 mmol) in dry carbon tetrachloride (80 ml) was refluxed in the presence of benzoylperoxide (50 mg, 0.2 mmol, 3 mol %) and light for 12-16 hours. The reaction mixture was then cooled to room temperature, succinimide was removed by filtration and the solvent was evaporated on a rotary evaporator. The crude product was chromatographed [benzene:ethylacetate (6:1)] to give the pure bromo product, **1a**.

Anal. Calcd. for $C_8H_9ON_2Br$: C, 41.95; H, 3.96; N, 12.23. Found : C, 42.21; H, 3.87; N, 12.51.

Compound (**2**) Compound 2-methyl-6-(4-nitrobenzoylamino)-pyridine was also brominated by this procedure yielding **2a** in 25% yield and **2b** in 68% yield.

In the Presence of Water.

To a stirred solution of 2-acetamido-6-methylpyridine (1g, 6.6 mmol) in carbon tetrachloride containing water (0.17 ml, 9.9 mmol, 15 equivalents), was added *N*-bromosuccinimide (crystallised) (1.42 g, 8.0 mmol) and benzoyl peroxide (50 mg, 0.20 mmol, 3 mol %). The mixture was refluxed in the presence of light and the reaction was completed within 1.5 hour. The solvent was evaporated *in vacuo* and the reaction mixture was purified chromatographically using benzene/ethylacetate 96:1). 2,6-Dimethylpyridine and 2,7-dimethylnapthyridine were brominated by this method.

In Acetonitrile.

To a solution of 2-acetamido-6-methylpyridine (0.1 g, 0.66 mmol) in 5 ml of acetonitrile was added *N*-bromo-succinimide (0.14 g, 0.8 mmol). The reaction was stirred at room temperature in presence of light for 2-3 hours. The solvent was evaporated under reduced pressure and CCl_4 was added. The solid was filtered and evaporation of carbon tetrachloride gave the pure brominated compound. This procedure was followed for the bromination of 2,6-dipivaloylaminopyridine.

In Presence of Perchloric Acid.

To a solution of 2-acetamido-6-methylpyridine (0.1 g, 0.66 mmol) in CCl_4 containing perchloric acid (0.4 ml, 0.66 mmol) was added *N*-bromosuccinimide (0.14 g, 0.8 mmol) and benzoylperoxide (3 mol %). The mixture was refluxed in the presence of light for 5 hours. The solvent was then neutralized with saturated $NaHCO_3$ solution and washed with water. The organic solvent was evaporated *in vacuo* and was purified by column chromatography using benzene/ethylacetate (6:1) as the mobile phase to give **1a**.

Anal. Calcd. for $C_6H_6N_2Br_2$: C, 27.07; H, 2.27; N, 10.50. Found: C, 27.33; H, 2.89; N, 10.61.

2-*N*-Acetylamino-6-acetoxymethylpyridine (**1d**).

A mixture of compounds **1a** and **1b** (50 mg) was refluxed in dry dimethylformamide under a nitrogen atmosphere for 12 hours at 80-90 °C. The mixture was then poured into water and thoroughly extracted with dichloromethanne. The solution was dried with anhydrous sodium sulphate and was evaporated *in vacuo*. Purification by column chromatography using benzene:ethylacetate (6:1) gave compound **1d** in 75% yield (6 mg) and 41 mg compound **1a**. Hence the presence of compound **1b** in the mixture estimated was 9 mg and the overall yield of **1b** varied from 10-15%. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 8.45 (s, -NH-), 8.17 (d, 1H, J = 8 Hz), 7.75 (t, 1H, J = 8 Hz), 7.10 (d, 1H, J = 8 Hz), 5.11 (s, 2H), 2.23 (s, 3H), 2.17 (s, 3H).

2-Amino-6-hydroxymethylpyridine (**7c**).

To a stirred solution of 2-*N*-phthalimido-6-bromomethyl-pyridine **7a** (100 mg, 0.32 mmol) in dry ethanol, sodium acetate was added along with a catalytic amount of sodium iodide. The mixture was refluxed under a nitrogen atmosphere. Conversion of the starting material to the product was monitored by tlc. After stirring 15 hours the solvent was evaporated to dryness and ethylacetate was added. The solution was then passed through a silica gel bed to remove inorganic materials. Ethylacetate was evaporated *in vacuo* and to a warm ethanolic suspension of the crude acetate product **7b** (without characterising) hydrazine hydrate (0.68 mmol) was added. The solution was stirred in an oil bath and conversion was monitored by tlc. The mixture was poured into water and was extracted with chloroform. After evaporation of the solvent the crude product was purified by column chromatography using 10% methanol in chloroform as eluent to give the pure product **7c** in 46-50% yield (18-19 mg).

Acknowledgement.

We thank Department of Science and Technology and CSIR, Government of India for previous financial support. We also thank IIT, Kharagpur, IICB, Calcutta for NMR (Bruker AM 200 and 300 respectively) and IACS, Calcutta for elemental analysis.

REFERENCES AND NOTES

[1a] P. M. Windscheif and F. Vogtle, *Synthesis*., 87, (1994); [b] S. Mataka, M. Kurisu, K. Takahashi and M. Tashiro, *J. Heterocyclic Chem.*, **21**, 1157 (1984).

[2a] A. Kleemann, *Chem. Ztg*., 387 (1997); [b] H. Beschke, A. Kleenmann, W. Claus, W. Kurze, W. Mathes, K. Mathes and S. Habersang, *Ullmanns Encyklopadie der technischen Chemie*., Verlag Chemie, Weinheim, Deerfield Beach, Florida, Bd. **19**, 592 (1980).

[3] J. Barbera, E. Melenddez, P. Romero and J. L. Serrano, *Mol. Cryst. Liq. Cryst*., **126**, 259 (1985).

[4a] S. P. Goswami and R. Mukherjee, *Tetrahedron Lett*., **38**, 1619 (1997); [b] S. P. Goswami and K. Ghosh, *Tetrahedron Lett*., **38**, 4503 (1997); [c] S. P. Goswami, K. Ghosh and S. Dasgupta, *Tetrahedron*., **52**, 12223 (1996); [d] S. P. Goswami, K. Ghosh and S. Dasgupta, *J. Org.*

Chem., **65**, 1907 (2000); [e] S. Goswami and A. K. Mahapatra, *Tetrahedron Lett*., **39**, 1981 (1998).

[5] W. Offermann and F. Vogtle, *Synthesis*., 272 (1997).

[6a] H. Schmidt, *Helv. Chim. Acta*., **29**, 1144 (1946); [b] V. Paul, A. Sudalai, T. Daniel and K. V. Srinivasan, *Tetrahedron Lett*., **35**, 7055 (1994); [c] R. H. Mitchell, Y. H. Lai and R. V. Williams, *J. Org. Chem.*, **44**, 473 (1979); [d] R. S. Coleman and E. B. Grant, *J. Am. Chem. Soc.*, **116**, 8795 (1994).

[7] J. S. Pizey, In "Synthetic Reagents", Vol. **II**, John Wiley & Sons, New York, N.Y., 1974, Pp 1-63.

[8a] M. C. Carreno, J. L. G. Ruano, G. Sanz., M. A. Toledo and A. Urbano, *J. Org.Chem*., **60**, 5328 (1995); [b] M. C. Carreno, J. L. Garcia Ruano, G. Sanz, M. A. Toledo and A. Urbano, *Synlett*, 1241 (1997).

[9] H. Shaw, H. D. Perlmutter and C. Gu, *J. Org. Chem*., **62**, 236 (1997).

[10] R. Adams and A. W. Schrecker, *J. Am. Chem. Soc*., **71**, 1186 (1949).

[11] R. P. Mariclla and E. P. Belcher, *J. Am. Chem. Soc*., **74**, 1916 (1952).

[12a] C. J. Chandler, L. W. Deady, J. A. Reiss and V. Tzimos, *J. Heterocyclic. Chem*., **19**, 1017 (1982); [b] T. Ross Kelly, J. G. Bridger and C. Zhao, *J. Am. Chem. Soc*., **112**, 8024 (1990).

[13] S. P. Goswami, A. D. Hamilton and D. Van Engen, *J. Am. Chem. Soc*., **111**, 3425 (1989).

[14a] T. O. Yellin, P. N. Edwards and M. S. Large, (Imperial Chemical Industries Ltd.; ICI Americas, Inc.). Eur. Pat. Appl. EP 30,092; *Chem. Abstr*., **9** (1982), p69043r; [b] A. Asensio, B. Abarca, G. Jones, M. B. Hursthouse and K. M. Abdul Malik, *Tetrahedron*, **49**, 703 (1993).