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Alternative approach to the free radical bromination of oligopyridine benzylic-methyl group

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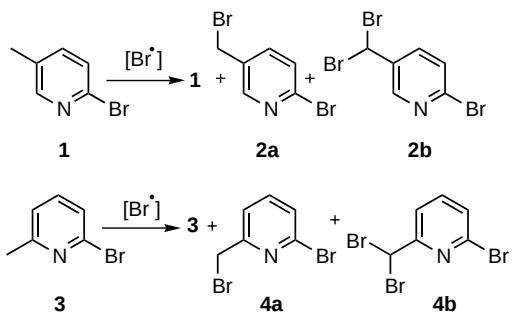
Abstract—We have undertaken a study on the influence of three solvents on the photobromination of two picolines. It shows that dichloromethane and benzene are better solvents than the classical carbon tetrachloride. The obtention of a good free radical bromination is described using aqueous biphasic media.

In our studies on oligopyridine based ligands[1] suitable for the encapsulation of lanthanide(III) salts, designed for time resolved fluorescence, such as podands[2,3] and cryptands,[4] we faced one major synthetic problem: the obtention in fair yields of benzylic bromide derivatives. These functions appeared to us as the most appropriate for an easy grafting of these oligopyridines on various preorganized molecules via simple nucleophilic substitution. Indeed, most of the syntheses described to obtain bipyridines based podands or cryptands used benzylic bromides precursors.[5]

The popular methods to obtain benzylic bromides are either a direct bromination of the benzylic methyl, or a deoxybromination of benzylic alcohol.[6] The latter route implies a multistep synthesis which is time consuming. The two-step bromination method, via the generation of the methyl anion, recently developed by Fraser[7] appears attractive. However, this method is incompatible with the presence of nucleophilic sensitive function on the molecule, such as an ester group.[1] The softer and simplest route remains the free radical bromination. The disadvantage of this direct bromination is concomitant formation of dibromomethyl derivatives, which reduces the yield of the desired bromomethyl and complicates the purification process. Moreover, it becomes a real synthetic problem when more than one benzylic methyl on the molecule has to be brominated.

To improve the free radical bromination of pyridine benzylic groups, we were inspired by the works of Vöglte and co-worker[8,9] in the early 1980s. Their results on the bromination of toluene type model substrates using *N*-bromosuccinimide (NBS) and several solvents, pointed out the strong influence of the solvent on the selectivity of the reaction. Moreover, they correlated their results to the reactivity–selectivity principle.[10] A good compromise has to be found to preserve a sufficient reactivity in order to brominate the benzylic methyl, and a high selectivity to avoid multiple bromination. They have shown that the classical condition for free radical bromination (NBS/CCl_4) of a benzylic methyl is not optimum, due to a high reactivity, inducing a low selectivity.

To apply Vöglte results to oligopyridine derivatives, we selected two models of picolines bearing, respectively, a benzylic methyl on the *meta* and *ortho* position of the nitrogen: 2-bromo-5-methylpyridine (**1**) and 2-bromo-6-methylpyridine (**3**). We present free radical bromination results of **1** and **3** under several experimental conditions



Scheme 1.

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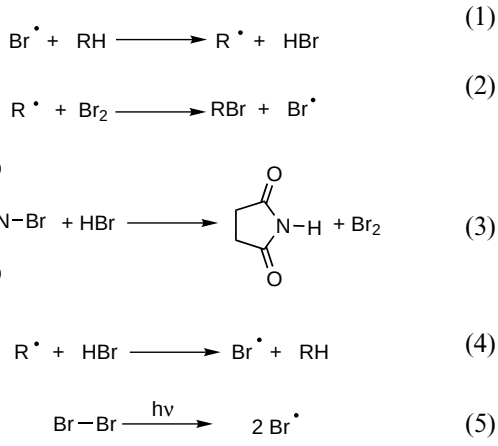
(Scheme 1). All the experiments were carried out using the same simple procedure and using easy to handle materials: a standard 150W halogen lamp. This lamp was placed at 5 cm from the reactor and its heat was used to reflux the solvent. In this study, we compare the yields of compounds obtained by reacting one equivalent of picoline and one equivalent of bromine donor. The yields of the compounds produced after the reaction were determined by ^{1}H NMR.[†]



We first carried out experiments varying the solvent with the most used bromine donor: *N*-bromosuccinimide, using AIBN as initiator. The small amount of $Br^{\bullet}$ then produced initiates the main propagation steps (Eqs. (1) and (2)). NBS has a double role: it provides a source of Br_2, in a low, steady state concentration, and consumes the liberated HBr by a ionic process[11] (Eq. (3)). The consumption of HBr avoids the inhibition of bromination (Eq. (4)).[12]

In order to choose the solvents for the bromination studies we tested some candidates described in the literature,[9] and we selected two of them to be compared with carbon tetrachloride: dichloromethane and benzene. Unfortunately, bromination in methyl formate described as the solvent inducing the highest 'selectivity', in the case of toluene family, was non-effective with picolines, due to a probable too low reactivity.

Under these conditions,[‡] CCl_4 appeared again to be the 'highest reactivity' solvent. After 3 h of irradiation, all the bromine was consumed. This reactivity seemed to be in opposition to 'selectivity'.[8] The yield of bromomethyl derivatives was similar to the concurrent solvents, but a large amount of dibromomethyl was produced (Table 1). For the bromination of **1**, the use of benzene appears to be the most appropriate method in order to obtain **2a** with a minimum of **2b** produced. Due to the toxicity of carbon tetrachloride and benzene, dichloromethane can probably be considered as the best choice. The same results were observed in the bromination of **3** (Table 2). The yields were slightly lower than for **1**, probably due to an interaction of the nitrogen lone pair near the methyl groups with the free radical bromination process.

The low yields of production of dibromomethyl compounds in the case of benzene in opposition to CCl_4, both having similar boiling points, indicate different reactivity of the hydrogen abstracting species. In presence of benzene, a bromine radical/arene π-complex is probably formed, similar to the complex observed with chlorine.[13,14] This complex is probably characterized by a different selectivity for the abstraction of a benzylic hydrogen (Eq. (1)). The good results obtained with dichloromethane are probably due to the low temperature of the reaction.

Water was described as an excellent medium for free radical reaction,[15] due to its remarkable non-reactivity towards radicals (OH bond resistancy to homolytic breaking). Unfortunately, the solubility of most organic compounds is limited in water. Very good results for the photobromination of toluene derivatives with bromine in water were observed.[15] In fact, toluene acts as its own solvent and consequently the reaction is

Table 1. Bromination of **1** with NBS

Solvent	CCl_4[d]	CH_2Cl_2[d]	C_6H_6[d]
1 (%)[a]	12	19	24
2a (%)[a]	66	69	67
2b (%)[a]	22	12	9
Br cons. (%)[b]	100	84	77
Ratio[c]	0.34	0.17	0.13

[a] Relative yields calculated from ^{1}H NMR spectra.
[b] Consumption of bromine corrected by the starting quantities of bromine donor.
[c] Ratio of **2b** over **2a**.
[d] Method A: average value for a minimum of three experiments.

Table 2. Bromination of **3** with NBS

Solvent	CCl_4[d]	CH_2Cl_2[d]	C_6H_6[d]
3 (%)[a]	20	26	26
4a (%)[a]	58	64	62
4b (%)[a]	22	10	12
Br cons. (%)[b]	93	77	78
Ratio[c]	0.38	0.16	0.19

[a] Relative yields calculated from ^{1}H NMR spectra.
[b] Consumption of bromine corrected by the starting quantities of bromine donor.
[c] Ratio of **4b** over **4a**.
[d] Method A: average value for a minimum of three experiments.

[†] Product analysis. In the ^{1}H NMR spectrum, the benzylic protons show up: for the methyl group at 2.28 for **1** and 2.52 ppm for **3**; for the bromomethyl group at 4.44 for **2a** and 4.49 ppm for **4a**; for the dibromomethyl group at 6.56 for **2b** and 6.57 ppm for **4b**. The values obtained in Table 1, were confirmed by HPLC analysis.

[‡] Method A: A mixture of bromo-methyl-pyridine (0.1 g, 0.58 mmol), NBS (0.115 g, 0.64 mmol) and a catalytic amount of AIBN in a pure organic solvent (10 mL) or in a biphasic medium (organic solvent/water, 10/10 mL) was lightened and refluxed using a halogen lamp (150W) for 3 h. The resulting organic layer was filtered through a short alumina (Act IV) column, and evaporated under reduced pressure. ^{1}H NMR analysis of the crude product gave the relative percentages.

operated in a biphasic medium. We decided to study the photobromination of our picolines in biphasic mixtures using NBS or Br_2 as bromine donors and our three reference solvents.

The results obtained in biphasic media, in the case of **1**, using NBS as bromine donors gave almost similar yields of **2a** as in absence of water, but the production of **2b** was lowered (Table 3). When bromine is used, the reaction is really convenient:[§] completed in only 30 min, no succinimide residues have to be eliminated and less dibromomethyl derivative is produced. In this case, the reaction is initiated by irradiation (Eq. (5)). The propagation steps take place in the organic phase and water seems to be a very efficient scavenger of the coproduct HBr (Eq. (1)). The abstraction of HBr prevents the reverse reaction (Eq. (4)) and thus accelerates the reaction. In the absence of water, we have observed few bromination compounds even after more than 2 days irradiation. When NBS is used, the abstraction of HBr produced by the aqueous phase seems not to interact with the ionic processes of the generation of bromine (Eq. (3)). This process probably takes place in water or at the interface. In fact the only difference is the slow liberation of Br_2 in the case of NBS. If large scale quantities have to be brominated, the use of a dropping funnel with a diluted organic solution of bromine could be a good alternative to NBS.

The study of the free radical bromination of **3** with NBS in the biphasic mixture shows almost similar yields as the monophasic case (Table 4). The yield differences between the bromination of **1** and **3** are enhanced with the use of bromine. Under these conditions, the presence of the nitrogen lone pair seems to have a significant action on the free radical process. These differences in the photobromination of methyl groups in the α or β position to the nitrogen was noticed when we applied these results to a more complicated oligopyridine.[1] The free radical bromination of ethyl 5-methyl-2,2′-bipyrine-6-carboxylate to its monobromoethyl derivatives could be raised from 56 (NBS, benzene) to 73% (Br_2, Benzene/H_2O), but not with the α-methyl isomer ethyl 6-methyl-2,2′-bipyridine-6-carboxylate.[1]

We can conclude from this study that the photobromination of picoline benzylic-methyl to obtain the corresponding bromomethyl derivative is more efficient in dichloromethane or benzene than in carbone tetrachloride. For environmental and toxical reasons the best solvent is probably dichloromethane. The use of an

Table 3. Bromination of **1** in biphasic media

Solvent	CCl_4/H_2O		CH_2Cl_2/H_2O		C_6H_6/H_2O	
Donor	Br_2[d]	NBS[e]	Br_2[d]	NBS[e]	Br_2[d]	NBS[e]
1 (%)[a]	21	13	25	13	27	29
2a (%)[a]	62	69	67	72	66	66
2b (%)[a]	17	18	8	15	7	5
Br cons. (%)[b]	96	96	83	92	79	79
Ratio[c]	0.28	0.26	0.12	0.20	0.10	0.08

[a] Relative yields calculated from ^1H NMR spectra.
[b] Consumption of bromine corrected by the starting quantities of bromine donor.
[c] Ratio of **2b** over **2a**.
[d] Method B: average value for a minimum of three experiments.
[e] Method A: average value for a minimum of three experiments.

Table 4. Bromination of **3** in biphasic media

Solvent	CCl_4/H_2O		CH_2Cl_2/H_2O		C_6H_6/H_2O	
Donor	Br_2[c]	NBS[d]	Br_2[c]	NBS[d]	Br_2[c]	NBS[d]
3 (%)[a]	30	23	34	19	37	30
4a (%)[a]	50	57	58	67	54	59
4b (%)[a]	20	20	7	14	9	11
Br cons. (%)[a]	90	89	72	86	72	75
Ratio[b]	0.40	0.36	0.12	0.21	0.16	0.19

[a] Calculated on the basis of the starting quantities of bromine.
[b] Ratio of **4b** over **4a**.
[c] Method B: average value for a minimum of three experiments.
[d] Method A: average value for a minimum of three experiments.

[§] Method B: To a refluxing mixture of bromo-methyl-pyridine (0.1 g, 0.58 mmol) in a biphasic medium (organic solvent/water, 10/10 mL) was added Br_2 (30 μL, 0.58 mmol). The mixture was then lightened and refluxed using a halogen lamp (150W) during 30 min. The solution was neutralized with a $NaHCO_3$ aqueous solution. The aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were dried with $MgSO_4$ and evaporated in vacuo. NMR analysis of the crude product gave the relative yields.

aqueous biphasic mixture of solvent and bromine has been shown to be a convenient synthetic procedure for the free-radical bromination of selected compounds.

Further applications of the results of this study on various oligopyridines are in progress.

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