Reactions of 4-(Trihalomethyl)quinazolines with Aliphatic Amines. Role of the Halogen Atom and of the Amine on the Reaction Pattern[1]

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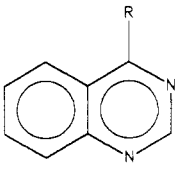
Activated aromatic or heteroaromatic compounds bearing a trihalomethyl group can react with nucleophiles according to several reaction patterns.[2] The factors that can influence the outcome of the reaction are (i) the nature of the aromatic nucleus, (ii) the relative position of the trihalomethyl group with respect to the activating group(s), (iii) the type of halogen atom, and (iv) the nature of the nucleophile.

Some time ago, we started an investigation on the reactivity of 4-(trihalomethyl)quinazolines toward nucleophiles, with the initial aim being to assess the leaving-group ability of the CX_3 groups in an aromatic nucleophilic substitution.

In fact, we found that 4-(trichloromethyl)quinazoline (1) reacts with MeO^- in MeOH[3] and OH^- in $MeCN/H_2O$[4] to give the expected products of aromatic nucleophilic substitution. On the other hand, we also found that 4-(tri-



1, R = CCl_3 6, R = OH
2, R = CBr_3 7, R = $CONHC_3H_7$
3, R = NHC_3H_7 8, R = $CONC_4H_8$
4, R = NC_4H_8 9, R = $CHBr_2$
5, R = $CONC_5H_{10}$ 10, R = $C(NC_5H_{10})_3$

bromomethyl)quinazoline (2) can react with ketones and phenols as a brominating agent: ketones undergo bromination at the α position, and the phenols undergo aromatic bromination at the ortho and para positions.[5] In these cases, a nucleophilic attack occurs at a side-chain bromine atom. Compound 1 is completely unreactive in the same conditions.

We now report on a complete comparison of the reactivity of compounds 1 and 2 with aliphatic amines in acetonitrile. We chose propylamine as a primary amine and pyrrolidine and piperidine as secondary amines.

Table I. Reaction of 1 with Propylamine in MeCN at 42 °C

[amine], M	$10^4 \times k_{obsd}/[amine]$, M^{-1} s^{-1}
0.099	1.11
0.149	1.59
0.200	2.05
0.300	3.15
0.400	4.20
0.495	5.11

Table II. Reaction of 1 with Pyrrolidine in MeCN at 42 °C

[amine], M	$10^5 \times k_{obsd}/[amine]$, M^{-1} s^{-1}
0.213	2.50
0.309	4.75
0.411	8.19
0.533	10.5

Results and Discussion

It is useful to briefly outline the different possible pathways for the reactions of a 4-(trihalomethyl)-quinazoline with nucleophiles: (a) attack at position 2 of the quinazoline ring, with the reversible formation of a σ adduct; (b) attack at position 4, with the formation of the σ adduct and the ensuing departure of the CX_3^- group (in a protic solvent, the formation of a covalent solvation adduct is also possible[3]); (c) attack and substitution at the aliphatic carbon atom; and (d) attack at the halogen atom (halogenophilic substitution)[6].

In the reaction of compounds 1 and 2, we have observed all but the first of these possibilities, depending on the nature of the halogen atom and the amine.

Reactions of 1. Compound 1 reacts at room temperature in acetonitrile with an excess of propylamine and pyrrolidine to yield the corresponding products of aromatic nucleophilic substitution, i.e., compounds 3 and 4, respectively. To our surprise, the reaction of 1 with piperidine, carried out under the same conditions, was completely different: it was much slower, and no product of aromatic nucleophilic substitution by piperidine was observed. Instead, products 5 and 6 were isolated. Amide 5 is the final product of an aliphatic substitution at the CCl_3 carbon atom. The parent compound of amide 5 could be orthoamide 10, but any attempt to isolate it, by using anhydrous reagents, failed. 4-Hydroxyquinazoline (6) is the product of an aromatic substitution by water probably present in the reaction mixture.

The different reaction pattern and the different reaction time observed for the reaction of 1 with piperidine imply that the aromatic nucleophilic substitution reaction by this amine is much slower than that with the other two amines that exhibit the same reaction pattern and comparable reactivity. As a consequence of this lower reactivity, other reaction pathways, like the aliphatic substitution and the reaction with water, emerge. At first, this different behavior of pyrrolidine and piperidine is puzzling. These two amines, in fact, show very similar properties such as their pK_a values[7] and the rates of nucleophilic attack on aromatic carbon.[8] However, a similar huge difference between pyrrolidine and piperidine was reported by Bunnett et al. for the reaction of those amines with 2,4-dinitro-1-naphthyl ethyl ether in DMSO.[8] Whereas the rates of the attack of these amines are comparable, the rates for the departure of the ethoxy moiety from the intermediate σ adduct is 11 000 times greater for the pyrrolidine system.

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According to the authors' hypothesis, this difference arises from the different steric interaction between the amino moieties and the peri 8-hydrogen of the naphthalene ring. Since the geometry of the quinazoline system strictly resembles that of the naphthalene system, we believe that also in our case the different behavior of pyrrolidine and piperidine arises from such an interaction.

However, in terms of the addition–elimination mechanism,[9] the second step of a nucleophilic aromatic substitution (i.e., the departure of the nucleofuge from the σ adduct) can control the observed reactivity only if it is the rate-limiting step. Under this condition, base catalysis is usually observed in the reactions with amines.[10] In order to check if the second step were rate limiting, some kinetic experiments were carried out on the reaction of **1** with propylamine and pyrrolidine in MeCN. The results, reported in Tables I and II, indicate that, for both the amines, the second-order rate constant k_A ($=k_{obsd}/[amine]$) shows a linear dependence on the amine concentration according to eq 1:

$$k_A = k' + k''[amine] \quad (1)$$

These kinetic results clearly indicate that the reaction of compound **1** with both the amines is base catalyzed, thus implying that the second step of the aromatic nucleophilic substitution is rate limiting. The observed base catalysis for the reaction of **1** with propylamine is noteworthy since examples of base catalysis in aromatic nucleophilic substitution reactions with primary amines are rare and are usually observed in nonpolar solvents.[10]

Reaction of 2. In contrast with the behavior of **1**, compound **2** reacts with the three amines to undergo mainly the nucleophilic aliphatic substitution reaction. In fact, amides **5**, **7**, and **8** are the main products isolated in the reaction of **2** with piperidine, propylamine, and pyrrolidine, respectively. A minor product, compound **9**, is also present in all the cases. Compound **9** is the product of a halogenophilic substitution: it derives from an attack of the nucleophile on the bromine atom of the CBr_3 group.

Therefore, putting aside the behavior of compound **1** with piperidine that, as explained above, is peculiar to this amine, the first observation that can be made from the experimental data is that compound **1** prefers to undergo aromatic substitution, whereas compound **2** prefers the aliphatic substitution. The second observation is that **2** is more prone than **1** to undergo the halogenophilic substitution. This agrees with the observation that compound **2** behaves as a brominating agent toward ketones and phenols whereas **1** does not.[5]

The different behavior of compound **1** and **2** can be rationalized by taking into account the different nature of the halogen atom of the trihalomethyl group. The role played by the halogen atom in the aromatic nucleophilic substitution is not straightforward because it may have different effects in the two steps of such a reaction. In the first step (attack of the nucleophile on the aromatic nucleus), compound **1** should be favored over **2** due to the more electronegative chlorine atom and to the smaller steric hindrance of the CCl_3 group[11] with a consequent smaller F strain. For the second step (departure of the CX_3^- moiety from the σ adduct), CBr_3^- should be a better nucleofuge group than CCl_3^- due to the lower basicity[12] of CBr_3^-. However, since in the reaction with amines the departure of the leaving group may not be a single step (base catalysis), the effect of the different halogen atom is not easily predictable. On the contrary, as far as the aliphatic nucleophilic substitution is concerned, it is well-known that the bromine atom is a better leaving group than chlorine in this type of reaction.[13] Therefore, the preference of compound **2** for this substitution is easily predictable.

Other instances of aliphatic nucleophilic substitution at the side chain of trihalomethyl-substituted aromatic or heteroaromatic compounds are known. For example, (trichloromethyl)benzene can be hydrolyzed to benzoic acid in water/acetone[2a] and 5-methyl-3-(trichloromethyl)-1,2,4-oxadiazole is converted to the corresponding carboxylate by treatment with KOH.[2b] In the reactions of other heteroaromatic derivatives with nucleophiles, an overall aliphatic substitution at the side chain is observed, but in these cases, a key role is played by the heteroatom; examples are given by 2-(trichloromethyl)imidazole,[2c] 2-(trifluoromethyl)quinoline,[2d] 2- and 3-(trifluoromethyl)-indoles,[2d] and 2,6-dichloro-3-(trichloromethyl)pyridine.[2e]

Coming back to the halogenophilic substitution, our observations agree with the usually observed order of reactivity for a halogenophilic process: I > Br ≫ Cl.[6] This behavior is supported by a simple PMO approach of the process.[6]

Experimental Section

Melting points are uncorrected. UV spectra were recorded on a Cary Model 219 instrument. ^1H NMR spectra were obtained with a Bruker WP 80 SY spectrometer. Mass spectra were obtained with a Kratos MS 80 spectrometer. TLC analyses were performed on Merck 60 F_{254} silica gel plates. Column chromatography separations were carried out on Merck 60 silica gel (70–230 mesh).

4-(Trichloromethyl)quinazoline (1) and 4-(tribromomethyl)quinazoline (2) were prepared as previously described.[3,5]

Reaction of 1 with Propylamine. To a stirred solution of 0.28 g of **1** (1.1 mmol) in 10 mL of acetonitrile was added 1 mL of propylamine (12 mmol) dropwise at room temperature. After about 3 h, the reaction was complete. TLC analysis (silica gel, 1:1 benzene/ethyl acetate) showed the presence of one product only. After the removal of the solvent, the residue was purified by column chromatography (silica gel, 1:1 benzene/ethyl acetate), to give 0.205 g of a white solid [mp (benzene) 131–131.5 °C; ^1H NMR (CD_3COCD_3) δ 1.0 (pseudotriplet, 3 H, $NCH_2CH_2CH_3$), 1.75 (pseudosextet, 2 H, $NHCH_2CH_2CH_3$), 2.85 (s, 1 H, NH), 3.60 (pseudoquartet, 2 H, $NHCH_2CH_2CH_3$), 7.3–7.8 (m, 3 H, H6–H8), 8.10 (2 m, 1 H, H-5), 8.50 (s, 1 H, H-2); UV (MeCN) λ_{max} 290, 315 nm; mass spectrum calcd for $C_{11}H_{13}N_3$ (M^+) m/e 187.110939, found 187.1104] identified as 4-(propylamino)quinazoline (**3**) (yield 96%).

Reaction of 1 with Pyrrolidine. The reaction was carried out as described above, starting from 0.25 g of **1** (1 mmol) and 1 mL of pyrrolidine (12 mmol), to give 0.190 g of a white solid [mp (CCl_4) 57.5–58.5 °C; ^1H NMR (CD_3COCD_3) δ 2.10 (m, 4 H, NCH_2CH_2), 3.90 (m, 4 H, NCH_2CH_2), 7.30–7.90 (m, 3 H, H6–H8), 8.25 (2 m, 1 H, H5), 8.55 (s, 1 H, H-2); UV (MeCN) λ_{max} 297, 324 nm; mass spectrum calcd for $C_{12}H_{13}N_3$ (M^+) m/e 199.110939, found 199.1109] identified as 4-(1-pyrrolidinyl)quinazoline (**4**) (yield 94%).

Reaction of 1 with Piperidine. To a stirred solution of 0.25 g of **1** (1 mmol) in 10 mL of MeCN was added 1 mL of piperidine (10 mmol). The reaction mixture was kept at room temperature and periodically checked by TLC (silica gel, 1:1 benzene/ethyl acetate). Within 8 days, the reaction was complete and a crystalline white solid was present at the bottom of the reaction flask. TLC analysis of the solution showed the presence of two main

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products. The solid was separated and was identified as piperidine hydrochloride (0.08 g). The reaction mixture, after the removal of the solvent, was subjected to column chromatography (silica gel, 1:1 benzene/ethyl acetate), and two products were obtained: the first one (0.06 g) [mp (petroleum ether) 90–91.5 °C; ^{1}H NMR (CD_3COCD_3) δ 1.65 (m, 6 H, $NCH_2CH_2CH_2$), 3.15 (m, 2 H, $NHCH_2CH_2CH_2$), 3.80 (m, 2 H, $NCH_2CH_2CH_2$), 7.50–8.00 (m, 4 H, H5–H8), 9.20 (s, 1 H, H-2); mass spectrum calcd for $C_{14}H_{15}N_3O$ (M^+) m/e 241.121 503, found 241.12104] was identified as 4-(1-piperidylcarbonyl)quinazoline (**5**) (yield 25%), and the second one (0.06 g) was identified as 4-hydroxyquinazoline[14] (**6**) (yield 41%).

Reaction of 2 with Propylamine. To a stirred solution of 0.26 g of **2** (0.68 mmol) in 50 mL of MeCN, was added 0.60 mL of propylamine (7.25 mmol) dropwise at room temperature. Within about 18 h, the reaction was complete. A TLC analysis (silica gel, 1:1 benzene/ethyl acetate) showed the presence of two products. The solvent was removed, and the residue was taken up with ethyl acetate. A white crystalline solid separated and was identified as propylamine hydrobromide (0.17 g). The residue was subjected to column chromatography (silica gel, 3:2 and 3:7 benzene/ethyl acetate), and two products were obtained: the first one (0.06 g) was identified as 4-(dibromomethyl)quinazoline[5] (**9**) (yield 30%), and the second one (0.1 g) [mp 54–56 °C; ^{1}H NMR (CD_3COCD_3) δ 1.00 (pseudotriplet, 3 H, $CONHCH_2CH_2CH_3$), 1.72 (pseudosextet, 2 H, $CONHCH_2CH_2CH_3$), 2.95 (s, 1 H, NH), 3.43 (pseudoquartet, 2 H, $CONHCH_2CH_2CH_3$), 7.50–8.00 (m, 3 H, H6–H8), 9.10–9.30 (m, 2 H, H2–H5); mass spectrum calcd for $C_{12}H_{13}N_3O$ (M^+) m/e 215.105 854, found 215.1053] was identified as *N*-propyl-4-quinazolinecarboxamide (**7**) (yield 68%).

Reaction of 2 with Pyrrolidine. To a stirred solution of 0.25 g of **2** (0.66 mmol) in 50 mL of MeCN was added 0.60 mL of pyrrolidine (7.22 mmol) dropwise at room temperature. Within 18 h, the reaction was complete. A TLC analysis (silica gel, 1:1 benzene/ethyl acetate) showed the presence of a main product together with a minor one. The latter was identified by comparison (TLC) as compound **9**. The reaction mixture, after the removal of the solvent, was subjected to column chromatography (silica gel, 1:1 benzene/ethyl acetate), and a white solid was obtained (0.08 g) [mp 95–97 °C; ^{1}H NMR (CD_3COCD_3) δ 1.85 (m, 4 H, $CONCH_2CH_2$), 3.20 (m, 2 H, $CONCH_2CH_2$), 3.60 (m, 2 H, $CONCH_2CH_2$), 7.50–8.10 (m, 4 H, H5–H8), 9.20 (s, 1 H, H-2); mass spectrum calcd for $C_{13}H_{13}N_3O$ (M^+) m/e 227.105 854, found 227.105 25], identified as 4-(1-pyrrolidinylcarbonyl)quinazoline (**8**) (yield 53%).

Reaction of 2 with Piperidine. To a stirred solution of 0.25 g of **2** (0.66 mmol) in 50 mL of MeCN was added 0.65 mL of piperidine (6.6 mmol) dropwise at room temperature. Within 24 h, the reaction was complete. A TLC analysis (silica gel, 1:1 benzene/ethyl acetate) showed the presence, together with a major product, of a very small amount of compound **9**. The solvent was removed, and the residue was taken up with ethyl acetate. A crystalline white solid separated (0.3 g) and was identified as piperidine hydrobromide. The residue was purified by column chromatography (silica gel, 1:1 benzene/ethyl acetate), and a white solid (0.13 g), identified as compound **5** (yield 82%), was obtained.

Kinetic Measurements. The kinetic measurements for the reaction of **1** with propylamine and pyrrolidine were carried out spectrophotometrically, at 42 °C, in the thermostated cell compartment of a Cary 219 instrument. The solvent (MeCN) was purified by distillation over P_2O_5, and the amines were purified by distillation over Na. A large excess of the amine was present so that the reactions occurred under pseudo-first-order conditions. The reactions were followed at 290 and 297 nm, wavelengths corresponding to absorbance maxima for compounds **3** and **4**, respectively.

Least-squares treatment of the data reported in Table I for the reaction of **1** with propylamine yields the following: slope = 1.02×10^{-3} M^{-2} s^{-1} (standard deviation = 1.2×10^{-5}), intercept = 6.60×10^{-6} M^{-1} s^{-1} (standard deviation = 3.8×10^{-6}), correlation coefficient = 0.9997. The same treatment of the data reported in Table II yields the following: slope = 2.58×10^{-4} M^{-2} s^{-1} (standard deviation = 7.7×10^{-6}), intercept = -2.96×10^{-5} M^{-1} s^{-1} (standard deviation = 7.7×10^{-6}), correlation coefficient = 0.9941.

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Nitromethylenation of *N*-Methylpyridinium Salts[1]

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Extensive NMR investigations on the ammonia adducts of quaternized azaheteroaromatics (pyridinium, isoquinolinium, pyrimidinium, and pyrazinium salts[2-6]) have shown that the addition occurs quantitatively at the position adjacent to the quaternary nitrogen, yielding 2-aminodihydroazines. For steric reasons *N*-*tert*-butylpyridinium salts also gave addition at the 4-position in quaternary salts.[7] The σ-adducts are easily oxidized by potassium permanganate to the corresponding *N*-alkyl-2-(4)-imino derivatives,[8] and therefore this amination–oxidation reaction forms an interesting new synthetic tool for the preparation of *N*-alkyl-2-iminoazines. The facile replacement of the ring hydrogen in azinium salts (S_NH reactions[8]) by the imino group prompted us to look into the possibility of S_NH replacement reactions by other nucleophilic species. It has been reported[9] that the nitromethide ion, formed from nitromethane and liquid ammonia at −10 °C or lower, can successfully compete with the liquid ammonia in the addition reaction, as evidenced by ^{1}H NMR spectroscopy. Thus we decided to study the addition/oxidation reaction of nitromethide with pyridinium salts in liquid ammonia.

The behavior of the disubstituted pyridinium salts 1,2-dimethyl- (**1a**), 1,3-dimethyl- (**1b**), 1-methyl-3-phenyl- (**1c**), 1,4-dimethyl- (**4a**), and 3-methoxy-1-methylpyridinium chlorides (**4b**) was investigated first. Treatment of solutions of **1a–c** in liquid ammonia, containing nitromethide, with potassium permanganate afforded the

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