Convenient Synthesis of Trichloromethyldihydroquinolines and -isoquinolines

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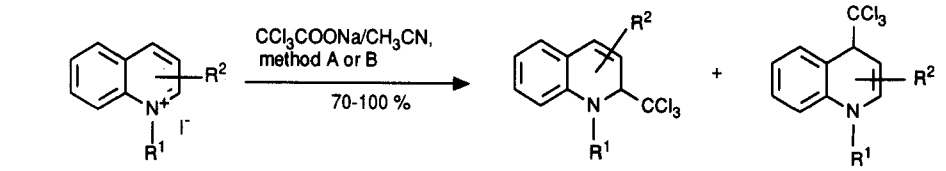
The reaction of a series of *N*-alkylquinolinium and -isoquinolinium iodides towards sodium trichloroacetate in acetonitrile has been investigated under reflux or ultrasonication. In all cases, addition of trichloromethyl anion was observed, and trichloromethyldihydroquinoline or -isoquinoline derivatives were obtained in good yields. Depending on the activation process, addition occured at the 2- or the 4-position with quinolines and at the 1-position with isoquinolines.

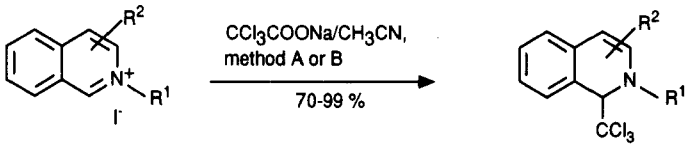
In connection with other work in our laboratory, *N*-methyltrichloromethyldihydro derivatives of quinoline and isoquinoline were needed. For the preparation of these compounds, we planned to take advantage of the great reactivity of *N*-alkylquinolinium and -isoquinolinium salts towards nucleophiles.[1] Some trichloromethyldihydropyridines had been obtained, in low to moderate yields as mixtures with cyclopropanation products, by the reaction of pyridinium chloride with chloroform and $Ba(OH)_2 \cdot H_2O$.[2] However, this method applied to quinoline salts did not lead to satisfactory results. A similar strategy using CX_3^- anions, which were generated in situ from haloform in alkaline media, led to good yields with pyridino derivatives, but low to moderate yields in the case of quinolines[3] (only 2 examples have been described). More recently,[4] under similar conditions, 2-trichloromethyl-1,2-dihydroquinoline derivatives were obtained in satisfactory yields from 1-methylquinolinium and 1,3- and 1,4-dimethylquinolinium salts, but the 4-trichloromethyl-1,4-dihydro derivative was obtained in low yield as the only product from 1,2-dimethylquinolinium iodide. One to three days were necessary to complete the reaction, and quinolones were isolated as side products. Looking for a more effective and convenient synthesis of all these models, we found that trichloromethyldihydroquinoline and -isoquinoline derivatives can be easily prepared through the reaction of heterocyclic iodides with sodium trichloroacetate in acetonitrile. The reaction is simply carried out in two ways: method A, stirring at the reflux temperature of the solvent; method B under ultrasonication, which is well known to promote heterogeneous reactions.[5]

The behaviour of iodides **1–4** has been studied and the results are summarized in Scheme 1 and Table 1. With



R^1 = Me	R^2 = H	**1a**	**5a**	**6a**
	2-Me	**1b**	**5b**	**6b**
	3-Br	**1c**	**5c**	**6c**
	4-Me	**1d**	**5d**	**6d**
	2,3-benzo	**1e**	-	**6e**
R^1 = Et	R^2 = H	**2a**	**7a**	**8a**
	2-Me	**2b**	**7b**	**8b**
	3-Br	**2c**	**7c**	**8c**
	4-Me	**2d**	**7d**	**8d**

Method A: at reflux
Method B: under sonification



R^1 = Me	R^2 = H	**3a**	**9a**
	3,4-benzo	**3b**	**9b**
R^1 = Et	R^2 = H	**4a**	**10a**
	3,4-benzo	**4b**	**10b**

Method A: at reflux
Method B: under sonification

Scheme 1

Table 1. Trichloromethylation of Compounds **1–4**

Substrate	Method[a]	Reaction Time (h)	Product (Ratio)	Total Yield (%)
1a	A	1	**5a/6a** (67 : 33)	100
1a	B	2	**5a/6a** (100 : 0)	70
1b	A	1	**5b/6b** (0 : 100)	97
1b	B	2	**5b/6b** (84 : 16)	70
1c	A	1	**5c/6c** (74 : 26)	95
1c	B	2	**5c/6c** (89 : 11)	96
1d	A	1	**5d/6d** (83 : 17)	72
1d	B	2	**5d/6d** (100 : 0)	92
1e	A	1	**6e**	90
1e	B	2	**6e**	90
2a	A	1	**7a/8a** (40 : 60)	82
2a	B	2	**7a/8a** (100 : 0)	90
2b	A	1	**7b/8b** (0 : 100)	82
2b	B	2	**7b/8b** (36 : 64)	72
2c	A	1	**7c/8c** (75 : 25)	86
2c	B	2	**7c/8c** (76 : 24)	65
2d	A	1	**7d/8d** (70 : 30)	70
2d	B	2	**7d/8d** (100 : 0)	90
3a	A	1	**9a**	93
3a	B	2	**9a**	98
3b	A	1	**9b**	84
3b	B	2	**9b**	85
4a	A	1	**10a**	87
4a	B	2	**10a**	72
4b	A	1	**10b**	99
4b	B	2	**10b**	80

[a] A, at reflux; B, with sonication.

Table 2. Physical Data for Compounds **5–10**[a]

Product	mp (°C)	IR, $\nu_{C=C}$ (cm^{-1})
5a	68	1635
5b	74	1646
5c	54	1620
5d	–	1653
6a	–	1650
6b	–	1655
6d	–	1660
6e	222	–
7a	–	1635
7b	–	1646
7c	61	1618
7d	78	1654
8a	–	1645
8b	–	1655
9a	80	1615
9b	86	–
10a	79	1615
10b	120	–

substrates **1–2**, which contain a quinoline moiety, competition occurred between addition of the trichloromethyl anion at the 2- or 4-position, leading to **5–8**. As shown in Table 1, the regiochemistry of the reaction depends on the activation process. This is well demonstrated by 2-methylquinolinium iodides **1b** and **2b**, which led specifically to the 2-addition products **(5b,7b)** under ultrasonication, and to the 4-addition products **(6b, 8b)** under reflux. As mentioned above, only the last compound had been previously obtained, in 24% yield.[4] Isoquinolinium and phenanthridinium iodides led to **9–10** in very good yields whatever the method used. However, the purity of the products was always higher using method B, which avoids their oxidation during the reaction.

According to the literature,[6] the overwhelming majority of nucleophiles add to 1-alkylquinolinium salts at the 2-position where the positive charge is higher; the inductive effects being greater there than at the 4-position. The question of the orientation of the attacking nucleophile at the two possible centers C-2 and C-4 of pyridines and quinoline has been discussed many times before.[1] Our results, especially those obtained under ultrasonication, suggest that the reaction is kinetically controlled, leading to addition at the 2-position. Under heating in acetonitrile solution, the 2-trichloromethyl derivatives **5a** and **7a** are converted into the 4-trichloromethyl isomers **6a** and **8a**. However, the isomerization is slow and never complete, even after 8 hours of reaction. Increasing the reaction time leads to partial side oxidation of the products. It is worth noting that in nonpolar solvents such as carbon tetrachloride the isomerization does not occur. In contrast, the 2–4 transposition is very easy with **5b** and **7b**, showing the influence of steric hindrance at the 2-position. With the 3-bromoquinoline derivatives, we did not succeed in isomerizing **5c** and **7c** into **6c** and **8c**, which could be due to the steric hindrance of the bromine atom. Indeed, during purification of the isomeric reaction mixture by liquid chromatography (Al_2O_3), degradation occured, and **6c** and **8c** were obtained in only 9 and 10% yield instead of the 25 and 22% initially present. Moreover, during NMR analysis in $CDCl_3$ or C_6D_6 solution, we observed a rapid conversion of **6c** and **8c** into insoluble products identified as the ion pairs **11** and **12** on the basis of NMR data. In particular, the ^1H NMR spectra exhibit for H-2 and H-3 two doublets (1 H, $J = 6.2$ Hz) at $\delta = 9.8$ and 8.8, as observed in the lepidine methiodide **1d** (2 d, $\delta = 9.4$ and 8.1, $J = 6.0$ Hz). These data are consistent with those reported for 4-substituted quinolinium chloride, obtained by a spontaneous aromatization of *N*-methyl-1,2-dihydroquinolines in CCl_4 or $CHCl_3$ solution.[7] In our case, the 2-trichloromethyl isomers **5c** and **7c** are very stable even in solution.

The isomerization can be interpreted as a thermodynamic process via the heterolytic dissociation of the 2-trichloromethyl compound, leading to a trichloromethyl anion–quinolinium cation pair, as proposed in the cases of trichloromethyl-[3], acetonyl-[8] or cyanodihydropyridines[9] and with cyano-[10] or (indol-3-yl)dihydroquinoline[11] in acetonitrile solution. Indeed, molecular mechanics (MM2 and M3) as well as CNDO calculations showed the greater stability of the 4-trichloromethyl isomers. We assumed that the heterolytic dissociation leading to the ion pair is only possible upon heating, and easier according to the nitrogen-substituent (Et > Me) and the ring-substituent (2-Me > 3-Br > H > 4-Me).

The structure assignments are based on satisfactory elemental analysis, IR spectra and ^1H and ^{13}C NMR spectra. The regiochemistry of the reaction can be unequivocally determined by ^1H NMR data[12] only in the cases of the unsubstituted compounds (Table 3). In the 2-trichloromethyl isomers **(5a, 7a)**, the 3,4-bond is olefinic in

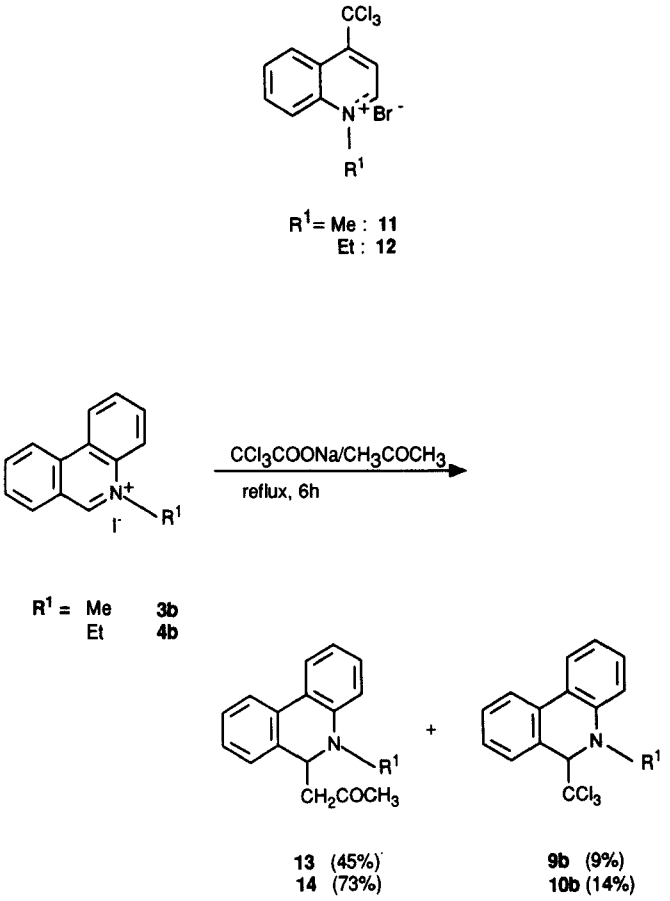
Table 3. ^{1}H NMR Data [δ, J (Hz)] for Compounds **5–12** ($CDCl_3$/TMS)

Product	CH_3	CH_2	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$	J
5a	3.4 (s)	–	–	4.8 (d, J = 5.7)	6.0 (dd, J = 5.7, 9.3)	6.9 (d, J = 9.7)	7.1 (dd)	6.8 (d)	7.3 (ddd)	7.0 (d)	7.4	7.6	7.8	1.5 (5, 7)
5b	2.0 (s) 3.3 (s)	–	–	–	5.8 (d, J = 9.8)	6.4 (d, J = 9.8)	7.0 (dd)	6.8 (dd)	7.2 (ddd)	6.8 (d)	7.5	7.4	8.4	1.6 (5, 7)
5c	3.5 (s)	–	–	5.0 (s)	–	7.3 (s)	7.0 (dd)	6.9 (dd)	7.3 (ddd)	6.9 (d)	7.0	7.0	7.7	1.2 (5, 7)
5d	2.2 (dd, J = 1.1, 0.8), 3.4 (s)	–	–	4.7 (dq, J = 5.9, 0.8)	5.9 (dq, J = 5.9, 1.1)	–	7.3 (dd)	6.9 (ddd)	7.3 (ddd)	6.8 (dd)	7.6	7.4	8.6	1.6 (5, 7) 1.2 (6, 8)
6a	3.2 (s)	–	–	6.9 (d, J = 7.6)	5.0 (dd, (J = 5.8, 7.6)	4.5 (d, J = 5.4)	7.5 (d)	7.0 (dd)	7.4 (dd)	6.9 (d)	7.6	7.6	8.3	
6b	2.2 (s) 3.3 (s)	–	–	–	4.9 (d, J = 5.8)	4.5 (d, J = 5.8)	7.6 (dd)	7.1 (dd)	7.4 (ddd)	7.1 (d)	7.6	7.4	8.4	1.4 (5, 7)
6d	1.9 (s) 3.2 (s)	–	–	6.4 (d, J = 7.8)	4.7 (d, J = 7.8)	–	7.6 (dd)	7.0 (ddd)	7.3 (ddd)	6.8 (dd)	7.9	8.0	8.3	1.5 (5, 7) 1.2 (6, 8)
6e	3.5 (s)	–	–	–	–	4.9 (s)	7.5 (dd)	7.1 (ddd)	7.4 (ddd)	7.1 (dd)	7.8	7.3	8.3	1.5 (5, 7) 1.0 (6, 8)
7a	1.2 (t, J = 7.0)	3.7 (dq, 1H, J = 14.0, 7.0), 4.2 (dq, 1H, J = 14.0, 7.0)	–	4.8 (d, J = 5.9)	6.1 (dd, J = 5.8, 9.6)	6.9 (d, J = 9.6)	7.1 (dd)	6.8 (dd)	7.3 (ddd)	7.0 (d)	7.4	7.4	8.2	1.4 (5, 7)
7b	1.2 (t, J = 7.0), 2.0 (s)	4.0 (dq, J = 14.4, 7.0)	–	–	5.8 (d, J = 9.6)	6.4 (d, J = 9.6)	7.1 (dd)	6.8 (ddd)	7.3 (ddd)	6.9 (dd)	7.9	7.4	8.2	1.1 (5, 7) 1.0 (6, 8)
7c	1.1 (t, J = 7.0)	3.5 (dq, 1H, J = 14.3, 7.1), 4.1 (dq, 1H, J = 14.3, 7.1)	–	4.9 (s)	–	7.2 (s)	7.1 (dd)	6.8 (ddd)	7.3 (ddd)	7.0 (dd)	7.5	7.3	8.2	1.4 (5, 7) 0.9 (6, 8)
7d	1.2 (t, J = 7.0), 2.2 (dd, J = 1.1, 0.7)	3.6 (dq, 1H, J = 14.8, 7.3), 4.1 (dq, 1H, J = 14.8, 7.0)	–	4.7 (dq, J = 6.0, 0.7)	5.8 (dq, J = 6.0, 1.1)	–	7.3 (dd)	6.8 (ddd)	7.3 (ddd)	6.9 (dd)	7.6	7.5	7.8	1.6 (5, 7) 1.2 (6, 8)
8a	1.3 (t, J = 7.1)	3.6 (dq, 1H, J = 14.6, 7.2), 3.8 (dq, 1H, J = 14.6, 7.2)	–	6.5 (d, J = 7.3)	5.0 (dd, J = 5.5, 7.3)	4.5 (d, J = 5.5)	7.5 (d)	7.0 (dd)	7.3 (dd)	7.0 (d)	7.6	7.5	8.4	
8b	1.3 (t, J = 7.0), 2.2 (s)	3.8 (dq, J = 12.5, 5.3)	–	–	4.9 (d, J = 5.7)	4.4 (d, J = 5.7)	7.6 (dd)	7.1 (ddd)	7.4 (ddd)	7.1 (dd)	7.6	7.3	8.4	1.5 (5, 7) 1.0 (6, 8)
8d	1.3 (t, J = 7.1), 1.9 (s)	3.6 (dq, 1H, J = 14.6, 7.2), 3.7 (dq, 1H, J = 14.6, 7.2)	–	6.4 (d, J = 7.7)	4.7 (d, J = 7.7)	–	7.6 (dd)	7.0 (ddd)	7.3 (ddd)	6.9 (dd)	8.0	7.0	8.4	1.5 (5, 7) 1.1 (6, 8)
9a	3.4 (s)	–	5.2 (s)	–	6.4 (d, J = 6.6)	5.8 (d, J = 6.6)	7.5 (d)	7.3 (dd)	7.4 (dd)	7.2 (d)	7.6	7.0	7.6	
9b[a]	3.5 (s)	–	5.2 (s)	–	–	–	7.0 (m, 1H), 7.0 (d, 1H, J = 8.1), 7.4 (m, 2H), 7.6 (m, 1H), 7.6 (d, 1H, J = 7.7), 7.9 (dd, 1H, J = 7.8, 1.2), 8.0 (d, 1H, J = 7.7)								
10a	1.2 (t, J = 7.1)	3.6 (dq, 1H, J = 14.3, 7.1), 3.7 (dq, 1H, J = 14.3, 7.1)	5.2 (s)	–	6.4 (d, J = 7.2)	5.8 (d, J = 7.2)	7.5 (dd)	7.3 (ddd)	7.4 (ddd)	7.1 (dd)	7.6	7.4	7.6	1.2 (5, 7) 1.2 (6, 8)
10b[a]	1.2 (t, J = 7.1)	3.7 (dq, 1H, J = 14.4, 7.1), 4.2 (dq, 1H, J = 14.4, 7.1)	5.2 (s)	–	–	–	7.0 (m, 1H), 7.1 (d, 1H, J = 8.0), 7.4 (m, 2H), 7.5 (m, 1H), 7.6 (d, 1H, J = 8.6), 7.9 (dd, 1H, J = 7.8, 1.1), 8.0 (d, 1H, J = 7.8)							
11[b]	4.7 (s)	–	–	9.8 (d, J = 6.2)	8.8 (d, J = 6.2)	–	8.7 (d)	8.2 (dd)	8.4 (dd)	8.9 (d)	8.8	7.2	8.5	
12[b]	1.7 (t, J = 7.1)	3.4 (q, J = 7.1)	–	9.7 (d, J = 6.3)	8.8 (d, J = 6.3)	–	8.8 (d)	8.2 (dd)	8.3 (dd)	9.0 (d)	8.7	7.6	8.6	

[a] With these compounds, which contain two aromatic rings, aromatic protons have not been assigned.
[b] In DMSO-d_6.

character, hence the proton coupling constant is close to that of a *cis* olefin, ie. 10 Hz. The 2,3-bond of the 4-trichlomethyl isomers **(6a, 8a)** is like that of an enamine and has $J_{2,3}$ of ca. 7.5 Hz. However, all the 2-trichloromethyl *N*-ethyl compounds showed two doublets of quartets separated by ca. 0.5 ppm for the two methylene protons, whereas the splitting is considerably smaller (0–0.1 ppm) with the 4-trichloromethyl isomers, clearly indicating the nature of the isomer. In contrast, ^{13}C NMR provides in all cases a clear understanding of the two isomers (Table 4). The most significant effects are observed for the carbon bonded to the CCl_3 group, which always resonates at $\delta = 72-81$ for all the 2-trichloromethyl isomers, and at $\delta = 58-59$ with the 4-trichloromethyl isomers. Only the acridine derivative deviates from these last values ($\delta = 63.2$), due to the effect of the adjacent aromatic ring. Generally, *N*-ethyl compounds lead to lower chemical shift values, **5b** and **7b** excepted, but in these cases we observed a quaternary carbon instead of a methine. It is worth noting that the N–CH_3 and N–CH_2 ^{13}C chemical shifts are always weaker in the 4-trichloromethyl derivatives than in the 2-trichloromethyl isomers.

In the case of **3a**, when using acetone instead of acetonitrile in the thermal process, a lower yield of **9a** resulted (53%). However, the yield increased to 93% when 2 equivalents of trichloroacetate were used, and reached 85% when 1 equivalent of water is added to the reaction mixture, thus demonstrating that this reaction does not require dry solvent. In acetone solution, phenanthridinium iodides **3b** and **4b** yield, respectively, the acetonyl derivatives **13** (45) and **14** (73%) along with **9b** (9) and **10b** (14%) (Scheme 2). Obtention of **13** and **14** is probably due to the weak solubility of the iodides in acetone. The resulting low concentration of substrate in the solution allows the trichloromethyl anion to abstract a proton from acetone, leading to acetone enolate. Compound **13** is identical to the product described by Dostál et al. from the reaction of 5-methylphenanthridinium iodide with potassium carbonate in acetone solution.[13]



Scheme 2

Table 4. ^{13}C NMR Chemical Shifts (δ) for Compounds **5–11** ($CDCl_3$/TMS)

Product	CH_3	CH_2	$\underline{C}HCCl_3$ $\underline{C}CCl_3$	CCl_3	Other C	CH sp^2
5a	42.9	–	75.7	105.8	121.7, 144.4	112.4, 116.7, 117.5, 126.6, 129.3, 130.1
5b	24.9, 35.2	–	72.0	109.9	121.3, 145.4	111.6, 117.5, 123.6, 127.1, 129.6, 129.8
5c	44.6	–	80.9	104.3	103.5, 122.9, 142.2	113.5, 118.8, 126.7, 130.0, 133.9
5d	19.2, 44.0	–	76.1	106.1	123.0, 135.8, 144.3	112.8, 114.8, 117.6, 123.9, 129.4
6a	38.2	–	58.7	107.2	117.1, 141.9	93.5, 111.9, 120.7, 128.9, 132.6, 136.5
6b	20.4, 32.9	–	59.0	107.2	118.1, 141.4, 143.2	93.4, 112.6, 120.4, 128.7, 132.5
6d	27.1	–	55.4	[a]	121.7, 141.6	99.5, 111.7, 120.4, 128.8, 130.2, 134.9
6e	33.4	–	63.2	105.0	118.6, 143.3	113.2, 120.2, 129.3, 132.9
7a	12.9	49.7	73.5	105.8	123.4, 142.7	115.0, 117.3, 118.2, 127.6, 129.3, 130.1
7b	14.0, 24.7	40.2	72.0	110.3	122.5, 142.9	112.7, 117.2, 123.7, 127.6, 129.5, 129.7
7c	13.2	50.7	78.3	104.2	104.2, 124.6, 140.8	115.8, 119.2, 126.8, 129.6, 133.8
7d	12.9, 19.3	49.5	73.4	106.3	24.7, 136.0, 142.6	115.0(2), 117.8, 124.2, 129.0
8a	13.4	45.0	58.7	107.3	117.3, 140.4	93.6, 111.9, 120.4, 128.7, 133.0, 135.2
8b	14.1, 20.4	39.3	58.9	107.7	118.0, 140.5, 141.6	93.7, 112.8, 120.2, 128.7, 132.9
8d	13.5	45.4	55.4	107.3	120.1, 140.2	99.7, 111.7, 120.1, 129.1, 130.5, 133.8
9a	45.4	–	77.7	106.2	120.7, 134.4	101.3, 123.8, 124.9, 129.2, 130.8, 135.6
9b	44.0	–	78.5	105.6	122.8, 126.8, 132.8, 143.1	114.2, 118.7, 122.6, 122.9, 126.4, 129.3, 129.5, 130.7
10a	15.0	52.4	75.8	106.4	112.4, 134.8	102.5, 123.7, 124.8, 129.1, 130.5, 133.9
10b	13.4	49.9	76.2	105.7	124.4, 127.7, 133.1, 141.6	116.2, 119.1, 123.0, 123.1, 126.5, 129.3(2), 130.5
11[b]	46.3	–	–	92.4	124.4, 140.1, 152.9	118.9, 120.1, 124.4, 127.8, 130.2, 135.3, 150.7

[a] Signal coincident with another.

[b] In CD_3OD.

Comparison with the literature[3,4] shows that the yields of the previously known derivatives **5a**, **5d**, **6b**, **7a**, and **10a** have been increased; other advantages of the present method are that the starting materials are easily available and the regiochemistry can be controlled according to the choice of the activation process. This is well-demonstrated by the good yields of the 2-addition products under ultrasonication even with 2-methylquinolinium iodides. Moreover, the manipulations and workup are simple and can be used for large-scale preparations.

Melting points were determined on a Mettler capillary apparatus and were uncorrected. IR spectra were obtained on a Perkin-Elmer 457 spectrophotometer. The NMR spectra were recorded on a Bruker AM 250 spectrometer ($CDCl_3$ solutions, TMS as internal standard). *J* values are given in Hz. Mass spectra were measured on an AEI MS 12 spectrometer. Elemental analyses were performed by service central d'analyse du CNRS (F-69390 Vernaison).

Liquid chromatography techniques (30 × 2 cm column) were employed to purify crude mixture using 70–230 mesh alumina (activity II–III). Ultrasound-promoted reactions were carried out in a common ultrasonic laboratory cleaner (Brandsonic 321) filled with thermostated water at 0–5 °C. The reaction flask was partially submerged in the sonicator water-bath in a place that produced maximum agitation.

All reagent grade chemicals were used as received. Methiodides and ethiodides were prepared according to literature procedures[14] by alkylation of the appropriate quinoline with alkyl iodide in acetone, **1e**, **3b** and **4b** excepted, which were prepared in CH_2Cl_2. The mixture was maintained at room temperature until the substrate had completely reacted, as monitored by TLC (SiO_2; Et_2O–CH_2Cl_2, 30:70). The precipitated salts were filtered and recrystallized. All data for the compounds are identical to literature data.[14]

Trichloromethylation of Methiodides and Ethiodides; General Procedure:

To a stirred solution of iodide (35 mmol) in MeCN (80 mL) was added sodium trichloroacetate (6.5 g, 35 mmol). The mixture was then stirred at reflux (method A) or sonicated (method B) until the starting material had completely reacted (Table 1), as monitored by TLC (SiO_2; MeOH–Me_2CO, 20:80). The reaction mixture was filtered through Celite and the filtrate evaporated to dryness. The residue was taken up in cyclohexane (80 mL), and insoluble materials, if present, were removed by filtration and analysed separately by NMR. The cyclohexane layer was concentrated under reduced pressure. The resulting residue was finally purified by liquid chromatography (Al_2O_3 activity II–III, 70–230 mesh; eluting typically with cyclohexane). In the case of ultrasonic reactions or with acridine, phenanthridine and isoquinoline derivatives, the crude product contained only one isomer, which was generally analytically pure. All the yields and analytical data for compounds **5–12** are reported in Tables 1–4. With the 3-bromoquinolinium iodides, we obtained a 75:25 mixture of 2- and 4-addition products (**5c/6c** from **1c** and **7c/8c** from **2c**). In the crude mixtures, the 4-addition products could be easily distinguished from the 2-isomers by ^1H NMR or IR spectroscopy (C=C stretch). During the purification by liquid chromatography, degradation occured, and **6c** and **8c** were obtained in only 9 and 10% yield instead of the 25 and 22% initially present. During NMR analysis in $CDCl_3$ or C_6D_6 solution, **6c** and **8c** were oxidized into **11** and **12**, and it was impossible to record their ^{13}C spectra. Spectral data of **5c**, **7c**, **11** and **12** are reported in Tables 2–4.

Compound **6c**:

IR (NaCl): $\nu = 1641\ cm^{-1}$ (vs, C=C).

TLC (SiO_2; C_6H_{12}): $R_F = 0.11$.

^1H NMR (60 MHz, $CDCl_3$): $\delta = 3.4$ (s, 3H), 4.8 (s, 1H, H-4), 7.0 (s, 1H, H-2), 7.0–7.5 (m, 4H).

Compound **8c**:

IR (NaCl): $\nu = 1637\ cm^{-1}$ (vs, C=C).

TLC (SiO_2; C_6H_{12}): $R_F = 0.12$.

^1H NMR (250 MHz, C_6D_6): $\delta = 0.6$ (t, 3H, $J = 6.9$), 2.6 (dq, 2H, $J = 14.0, 6.9$), 4.6 (s, 1H, H-4), 6.4 (s, 1H, H-2), 6.5 (d, 1H, $J = 8.0$), 6.6 (m, 1H), 6.9 (m, 1H), 7.1 (d, 1H, 8.2).

Reactions conducted in acetone at reflux (reaction time 6 h) were worked-up as described above. The reaction mixture was purified by flash chromatography (230–400 mesh silica gel). The trichloromethyl derivative (**9b**, **10b**) was eluted first using cyclohexane, then the acetonyl derivative (**13–14**) was obtained as a syrup using cyclohexane–CH_2Cl_2, 50:50. The spectrum of **13** was identical with data reported in literature.[13]

Compound **14**:

IR (NaCl): $\nu = 1712\ cm^{-1}$ (vs, C=O).

^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.3$ (t, 3H, $J = 7.1$), 1.9 (s, 3H, CH_3CO), 2.6 (d, 2H, CH_2CO, $J = 6.6$), 3.2 and 3.5 (2 dq, 2H, CH_2N, $J = 14.1, 7.1$), 4.9 (t, 1H, H-6, $J = 6.6$), 6.8–7.8 (m, 8H, ArH).

^{13}C NMR (62.86 MHz, $CDCl_3$): $\delta = 13.5$ and 31.7 (CH_3), 44.6 and 46.3 (CH_2), 57.4 (C-6), 114.5, 116.4, 123.0, 123.7, 126.0, 127.1, 127.8 and 129.2 (CH arom.), 123.3, 130.9, 135.8 and 143.6 (Cq arom.), 207.8 (C=O).

MS: $m/z = 265$ (M^+).

(1) For reviews, see:
Sidgewick, N.Y.; Sidgewick, F.R.S. *The Organic Chemistry of Nitrogen*; Clarendon: Oxford, 1966; p 718.
Dyke, S.F. *Adv. Heterocycl. Chem.* **1972**, *14*, 279.
Gurnos, J. *Quinolines*; Wiley: New York, 1982.
(2) Gundel, W.-H. *Z. Naturforsch., B Chem. Sci.* **1976**, *31*, 807.
(3) Duchardt, K.H.; Kröhnke, F. *Chem. Ber.* **1977**, *110*, 2669.
(4) Maeda, M. *Chem. Pharm. Bull.* **1990**, *38*, 2577.
(5) For reviews, see:
Boudjouk, P. *J. Chem. Educ.* **1986**, *63*, 427.
Suslick, K.S. *Modern Synthetic Methods*; Vol. 4; Springer: New York, 1986; p 1.
Luche, J-L. *Ultrasonics* **1987**, *25*, 40.
Goldberg, Y.; Sturkovich, R.; Lukevics, E. *Heterocycles* **1989**, *29*, 597.
(6) Joule, J.A.; Smith, G.F. *Heterocyclic Chemistry*; Van Nostrand Reinhold: New York, 1972.
(7) Tilak, B.D.; Subbaswami, K.N.; Gogte, V.N.; Das, K.G. *Indian J. Chem.* **1969**, *7*, 422.
(8) Kaválek, J.; Lyčka, A.; Macháček, V.; Šterba, V. *Collect. Czech. Chem. Commun.* **1976**, *41*, 67.
(9) Lyle, R.E.; Gauthier, G.J. *Tetrahedron Lett.* **1965**, 4615.
(10) Sidorov, E.O.; Matern, A.I.; Chupakhin, O.N. *Zh. Org. Khim.* **1980**, *17(2)*, 418; *Int. Ed. Engl.* **1981**, *17*, 357.
(11) Sheinkman, A.K.; Chmilenko, T.S.; Nezdiiminoga, T.N. *Khim. Geterotsikl. Soedin* (Engl. Trans.) **1984**, 991; *Chem. Abstr.* **1985**, *102*, 131890.
(12) Bramley, R.; Johnson, M.D. *J. Chem. Soc.* **1965**, 1372.
(13) Dostál, J.; Potáček, M.; Nechvátal, M. *Collect. Czech. Chem. Commun.* **1993**, *58*, 395.
(14) Doebner, O.; Miller, W. *Ber.* **1883**, *16*, 2464.
Duffin, C.F. *Adv. Heterocycl. Chem.* **1964**, *3*, 1.
Pollock, J.R.; Stevens, R. *Dictionary of Organic Compounds*; 4th ed., London 1965.
Zanker, V.; Cnobloch, H. *Z. Naturforsch., B Chem. Sci.* **1962**, *17*, 819.
Gurevitch, A.I.; Sheinker, Yu.N. *Zhur. Fiz. Chim.* **1959**, *33*, 883; *Chem. Abstr.* **1960**, *54*, 8285b.