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Highly efficient microwave assisted α-trichlorination reaction of α-methylated nitrogen containing heterocycles

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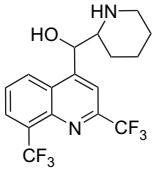
Abstract—A new methodology permitting the chlorination of different α-methylated nitrogen containing heterocycles into *N*-α-trichloromethylated derivatives is described here. The combination of microwave technology with a $PCl_5/POCl_3$ protocol has allowed to reach trichloromethyl derivatives with high yields in a few minutes.

1. Introduction

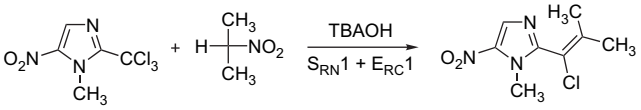
Trichloromethyl compounds are well-known precursors in the one-step synthesis of the corresponding trifluoromethyl structures, using fluorinating agents like SbF_5 or SbF_3.[1,2] Among trifluorinated structures, mefloquine can be mentioned as a major molecule of pharmaceutical interest (Scheme 1).



Scheme 1.

In order to optimize the global production of trifluoromethyl drug analogs, the efficient synthesis of the corresponding trichloromethyl substrates remains a preoccupation.

Aromatic α-trichloromethylated nitrogen containing heterocycles present another synthetic interest in the field of radical reactions, which are developed in our research team.[3] As shown in Scheme 2, trichloromethyl compounds, after being nitrated, are excellent substrates for consecutive $S_{RN}1$ and $E_{RC}1$ reactions with nitroalkane salts, leading to original vinyl chloride products.[4]



Scheme 2.

The methyl group trichlorination can be performed through radical mechanisms using *N*-chlorosuccinimide[5] or chlorine[6] with, respectively, purification and technical complications. Chupp's method[7] is also an original possibility for realizing this reaction in the case of methyl groups with acid protons, but has a more complicated protocol. Moreover, it presents real high yields when chloromethyl groups are transformed into trichloromethyl ones.

Kato[8–10] described another method concerning the specific trichlorination of a few α-methylated nitrogen containing heterocycles, using both phosphorus pentachloride and phosphorus oxychloride, providing medium yields, and requiring long reaction times.

Our laboratory being involved in the study of the microwave irradiation influence in organic chemistry,[3,11] we investigated the possibility of realizing such chlorination reactions through a microwave synthesis in order to optimize them and obtain the trichloromethyl derivatives in higher yields and much shorter reaction times. Applying this simple method, we studied the synthesis of various trichloromethyl compounds in quinoline, quinoxaline, quinazoline, benzoxazole, benzothiazole, and imidazo[2,1-*b*]thiazole series.

Keywords: Ionic polychlorination; Microwave assisted reactions; Nitrogen containing heterocycles.
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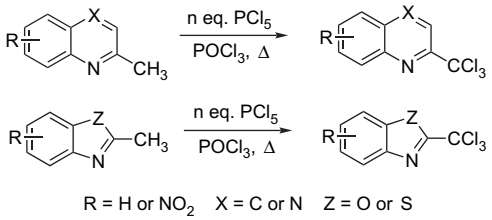
2. Results and discussion

From 1967 to 1981, Kato presented, in several publications,[8–10] a protocol permitting the trichlorination of the 'activated' methyl group in α-position of the sp^2 nitrogen atom in pyridine and quinoline series. This method uses phosphorus pentachloride as a powerful ionic chlorinating agent, and phosphorus oxychloride as a solvent, the reaction mixture being heated to reflux for a long time (from 12 to 60 h). The limitation of such a procedure rapidly appears because of the small or medium yields obtained (from 4 to 61%), depending on the substrate, considering the importance of reaction time needed.

In continuation of our studies exploring the chemical reactivity of α-trichloromethylated nitrogen containing heterocycles in electron transfer reactions, we tried to improve this chlorination synthesis procedure as far as obtaining the optimal procedure. We first started to work on the progression of this methodology in classical operating conditions, acting on two main parameters: reaction time and quantity of chlorinating agent used. For each substrate, repeating Kato's protocol, several times of reaction were investigated, and so was done for various quantities of PCl_5. The minimal required time for the reaction to proceed in a quantitative way is more often situated between 12 and 24 h. With longer times, the yield of the reaction decreases because of the highly reactive nature of the refluxed reaction mixture that damages the product previously formed. Optimal PCl_5 amount has then been determined. It always has to be superior to the number of hydrogen atoms that have to be substituted by chlorine ones, knowing that each PCl_5 molecule is able to liberate a single chlorine atom[9] for the chlorination reaction.

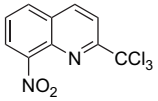
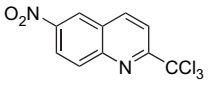
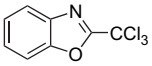
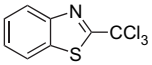
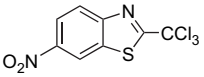
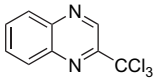
Consequently, in order to trichlorinate our substrates, the use of 4 equiv of PCl_5 usually provides the best yields, whereas some substrates require one more for being maximally transformed. Then, we decided to realize the same synthesis with a microwave assisted protocol using a microwave power of 800 W and studying the two same operating parameters. The global comparison between classical and microwave assisted conditions was then done, permitting to demonstrate the consequent contribution of the microwave technology in this synthetic approach (Scheme 3). Table 1 summarizes our optimal results in both conditions. It appears that in the microwave assisted reactions, times were massively reduced, and that the reaction yields were slightly increased or have, at least, remained constant.



Scheme 3.

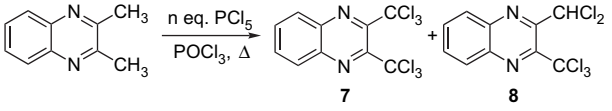
This single trichlorination reaction studied, we evaluated the possibility of performing a double trichlorination reaction in similar conditions, using 2,3-dimethylquinoxaline as a substrate (Scheme 4). Once more, we realized a parallel

Table 1. Optimal synthetic conditions and corresponding yields of monotrichlorination reactions

Compound number	Product	*n* equiv of PCl_5	Classical conditions[a]		MW conditions[b]	
			Time (h)	Yield (%)	Time (min)	Yield (%)
1		4	12	89	5	98
2		5	24	61	20	83
3		4	12	74	20	75
4		4	12	81	30	86
5		4	12	84	10	89
6		5	1.5	75	15	84

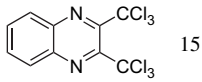
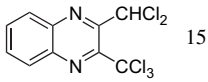
[a] Reaction mixture heated to reflux of $POCl_3$.
[b] Reaction mixture heated to reflux of $POCl_3$ under 800 W microwave irradiation.

optimization work on both classical and microwave assisted conditions. We synthesized the expected product 2,3-bis(trichloromethyl)quinoxaline **7**, but with lower yields compared to the products obtained with monomethylated substrates. Steric hindrance most probably explains this result, especially when we consider that the main product is 2-dichloromethyl-3-trichloromethylquinoxaline **8**. Here, the PCl_5 equivalent number has to be quite elevated so as to compete with steric limitations. Our optimal results are presented in Table 2.



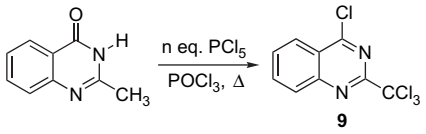
Scheme 4.

Table 2. Optimal synthetic conditions and corresponding yields of double trichlorination reaction

Compound number	Product	*n* equiv of PCl_5	Classical conditions[a]		MW conditions[b]	
			Time (h)	Yield (%)	Time (min)	Yield (%)
7		15	24	35	30	30
8		15	24	50	30	60

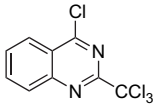
[a] Reaction mixture heated to reflux of $POCl_3$.
[b] Reaction mixture heated to reflux of $POCl_3$ under 800 W microwave irradiation.

Dehoff[12] and Smith[13] showed that the chlorination of 2-methylquinazolin-4-one with PCl_5 and PCl_3 logically affects the carbonyl group of the lactam ring, forming the aromatic tetrachlorinated product 4-chloro-2-trichloromethylquinazoline **9** with a maximum yield of 53%. We realized Kato's reaction on this substrate (Scheme 5), and optimized it. Table 3 presents the optimal results that we obtained in both operating conditions. Even without the use of microwaves, the yield of the reaction has been increased.



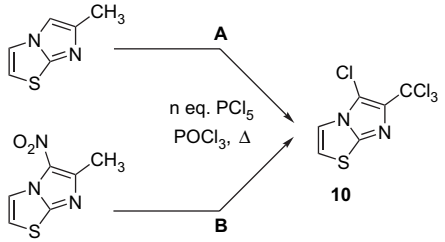
Scheme 5.

Table 3. Optimal synthetic conditions and corresponding yields for the synthesis of (**9**)

Compound number	Product	*n* equiv of PCl_5	Classical conditions[a]		MW conditions[b]	
			Time (h)	Yield (%)	Time (min)	Yield (%)
9		6	24	76	15	75

[a] Reaction mixture heated to reflux of $POCl_3$.
[b] Reaction mixture heated to reflux of $POCl_3$ under 800 W microwave irradiation.

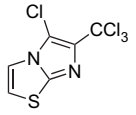
Finally, we developed this chlorination reaction on the imidazo[2,1-*b*]thiazole nucleus. As described in Scheme 6, 6-methylimidazothiazole (case A) and 6-methyl-5-nitroimidazothiazole (case B) were used as substrates for optimizing the trichlorination reaction in both classical and microwave operating conditions. Starting with two distinct substrates, the reaction product is the same compound: 5-chloro-6-trichloromethylimidazo[2,1-*b*]thiazole **10**.



Scheme 6.

In case A, the chlorination of the methyl group is associated to the chlorination of the 5-position. In case B, the same methyl trichlorination is accompanied with the substitution of the nitro group by a chlorine atom. Such behavior for a nitro group was already noted by Kato[10] who performed the same substitution on 2-methyl-3-nitroquinoline derivatives. Table 4 presents our optimal results for the two distinct synthesis access to **10** with both traditional and microwave assisted methodologies.

Table 4. Optimal operating conditions and corresponding yields for the formation of (**10**)

Compound number	Product	Method	*n* equiv of PCl_5	Classical conditions[a]		MW conditions[b]	
				Time (h)	Yield (%)	Time (min)	Yield (%)
10		**A**	5	24	86	10	85
		B	5	24	89	10	88

[a] Reaction mixture heated to reflux of $POCl_3$.
[b] Reaction mixture heated to reflux of $POCl_3$ under 800 W microwave irradiation.

3. Conclusion

The application of microwave assisted reaction to the chlorination protocol described by Kato proved to be a very efficient methodology in order to synthesize α-trichloromethylated nitrogen containing heterocycles. This very simple procedure provides high yields in a minimal time of reaction. Then, different types of chemical reactivity for the trichloromethyl group offer synthetic possibilities such as nucleophilic and polynucleophilic substitutions, vinyl chloride access and present a real pharmaceutical interest as the main synthetic pathway to trifluoromethyl compounds, very numerous among the therapeutic arsenal.

4. Experimental

4.1. General

Microwave assisted reactions were done in a multimode microwave oven ETHOS Synth Lab Station (Ethos start, Milestone Inc.). Melting points were determined with a B-540 Büchi melting point apparatus. ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Brüker ARX 200 spectrometer in $CDCl_3$ solution at the Faculté de Pharmacie de Marseille. ^1H and ^{13}C NMR chemical shifts (δ) are reported in parts per million with respect to $CDCl_3$ 7.26 ppm (^1H) and 77.16 ppm (^{13}C). Elemental analyses were carried out at the Centre de Microanalyses de la Faculté des Sciences et Techniques de Saint-Jérôme. The following adsorbent was used for flash column chromatography: silica gel 60 (Merck, particle size 0.063–0.200 mm, 70–230 mesh ASTM). TLC were performed on 5 cm×10 cm aluminum plates coated with silica gel 60F-254 (Merck) in appropriate solvent.

4.2. Experimental procedure

2-Trichloromethylquinoxaline (**6**) was described previously.[14]

4.2.1. General trichlorination procedure in classical operating conditions. The required equivalent number of phosphorus pentachloride and twice as much equivalents of phosphorus oxychloride were added to the substrate at 0 °C. The mixture was then heated to reflux and stirred for the adapted time, depending on the substrate. After cooling, the mixture was alkalinized with a saturated sodium carbonate solution and extracted with chloroform. Purification was

conducted by flash chromatography on a silica gel column eluting with dichloromethane–petroleum ether (1:1).

4.2.2. General microwave assisted trichlorination reaction. The required equivalent number of phosphorus pentachloride and twice as much equivalents of phosphorus oxychloride were added to the substrate at 0 °C. The mixture was placed in the microwave oven irradiating with 800 W, heating to reflux for the adapted time, depending on the substrate. After cooling, the mixture was alkalinized with a saturated sodium carbonate solution and extracted with chloroform. Purification was conducted by flash chromatography on a silica gel column eluting with dichloromethane–petroleum ether (1:1). Recrystallization wasn't necessary for compounds **1**, **2**, **7–10**, which were pure enough for elementary analysis.

4.2.3. 8-Nitro-2-trichloromethylquinoline (1). Pale yellow crystals, mp 127 °C. ^{1}H NMR (200 MHz; $CDCl_3$): δ 7.71 (1H, dd, J=8.0 and 7.8 Hz, H_6), 8.10 (2H, m, H_5, H_7), 8.18 (1H, d, J=8.8 Hz, H_4), 8.43 (1H, d, J=8.8 Hz, H_3). ^{13}C NMR (50 MHz; $CDCl_3$): δ 97.1 (C), 119.4 (CH), 124.8 (CH), 127.2 (CH), 128.4 (C), 131.4 (CH), 136.7 (C), 138.3 (CH), 148.2 (C), 159.0 (C). Anal. Calcd for $C_{10}H_5Cl_3N_2O_2$ (291.5): C, 41.20; H, 1.73; N, 9.61. Found: C, 41.55; H, 1.67; N, 9.99.

4.2.4. 6-Nitro-2-trichloromethylquinoline (2). Pale yellow crystals, mp 152 °C. ^{1}H NMR (200 MHz; $CDCl_3$): δ 8.24 (1H, d, J=8.9 Hz, H_4), 8.35 (1H, d, J=9.3 Hz, H_8), 8.53 (1H, d, J=8.9 Hz, H_3), 8.58 (1H, dd, J=9.3 and 2.5 Hz, H_7), 8.85 (1H, d, J=2.5 Hz, H_5). ^{13}C NMR (50 MHz; $CDCl_3$): δ 97.2 (C), 119.5 (CH), 123.8 (CH), 123.9 (CH), 126.8 (C), 132.1 (CH), 139.9 (CH), 146.8 (C), 147.9 (C), 160.5 (C). Anal. Calcd for $C_{10}H_5Cl_3N_2O_2$ (291.5): C, 41.20; H, 1.73; N, 9.61. Found: C, 41.70; H, 1.71; N, 9.84.

4.2.5. 2-Trichloromethylbenzoxazole (3). Colorless crystals, mp 61 °C (lit.[15]: 60 °C). ^{1}H NMR (200 MHz; $CDCl_3$): δ 7.47 (2H, m, H_5, H_6), 7.62 (1H, m, H_4), 7.86 (1H, m, H_7). ^{13}C NMR (50 MHz; $CDCl_3$): δ 86.0 (C), 111.4 (CH), 121.7 (CH), 125.7 (CH), 127.5 (CH), 139.9 (C), 151.5 (C), 160.0 (C).

4.2.6. 2-Trichloromethylbenzothiazole (4). Yellow crystals, mp 38 °C (lit.[15]: 37 °C). ^{1}H NMR (200 MHz; $CDCl_3$): δ 7.54 (2H, m, H_5, H_6), 7.91 (1H, m, H_4), 8.15 (1H, m, H_7). ^{13}C NMR (50 MHz; $CDCl_3$): δ 91.3 (C), 121.7 (CH), 124.8 (CH), 127.1 (CH), 127.2 (CH), 136.5 (C), 157.1 (C), 169.5 (C).

4.2.7. 6-Nitro-2-trichloromethylbenzothiazole (5). Yellow crystals, mp 110 °C (lit.[6]: 113 °C). ^{1}H NMR (200 MHz; $CDCl_3$): δ 8.26 (1H, d, J=9.1 Hz, H_4), 8.45 (1H, dd, J=9.1 and 2.3 Hz, H_5), 8.88 (1H, d, J=2.3 Hz, H_7). ^{13}C NMR (50 MHz; $CDCl_3$): δ 90.3 (C), 118.5 (CH), 122.5 (CH), 125.4 (CH), 136.7 (C), 146.1 (C), 155.6 (C), 174.8 (C).

4.2.8. 2,3-Bis(trichloromethyl)quinoxaline (7). Colorless crystals, mp 176 °C. ^{1}H NMR (200 MHz; $CDCl_3$): δ 7.95 (2H, m, H_6, H_7), 8.22 (2H, m, H_5, H_8). ^{13}C NMR (50 MHz; $CDCl_3$): δ 96.8 (2C), 128.9 (2CH), 133.1 (2CH), 138.8 (2C), 146.6 (2C). Anal. Calcd for $C_{10}H_4Cl_6N_2$ (364.9): C, 32.92; H, 1.10; N, 7.68. Found C, 32.99; H, 1.08; N, 7.68.

4.2.9. 2-Dichloromethyl-3-trichloromethylquinoxaline (8). Colorless crystals, mp 160 °C. ^{1}H NMR (200 MHz; $CDCl_3$): δ 7.81 (1H, s, $CHCl_2$), 7.93 (2H, m, H_6, H_7), 8.21 (1H, m, H_8), 8.30 (1H, m, H_5). ^{13}C NMR (50 MHz; $CDCl_3$): δ 67.1 (CH), 95.7 (C), 129.0 (CH), 129.8 (CH), 132.6 (CH), 132.7 (CH), 138.8 (C), 142.4 (C), 145.6 (C), 149.2 (C). Anal. Calcd for $C_{10}H_5Cl_5N_2$ (330.5): C, 36.35; H, 1.53; N, 8.48. Found C, 36.23; H, 1.49; N, 8.47.

4.2.10. 4-Chloro-2-trichloromethylquinazoline (9). White powder, mp 127 °C (lit.[12,13]). ^{1}H NMR (200 MHz; $CDCl_3$): δ 7.86 (1H, m, H_6), 8.08 (1H, m, H_7), 8.22 (1H, dd, J=8.5 and 0.5 Hz, H_5), 8.36 (1H, dd, J=8.4 and 0.6 Hz, H_8). ^{13}C NMR (50 MHz; $CDCl_3$): δ 95.9 (C), 122.9 (C), 126.0 (CH), 129.7 (CH), 130.6 (CH), 135.9 (CH), 150.2 (C), 159.9 (C), 164.0 (C).

4.2.11. 5-Chloro-6-trichloromethylimidazo[2,1-*b*]thiazole (10). Colorless crystals, mp 84 °C. ^{1}H NMR (200 MHz; $CDCl_3$): δ 7.02 (1H, d, J=4.5 Hz, H_2), 7.40 (1H, d, J=4.5 Hz, H_3). ^{13}C NMR (50 MHz; $CDCl_3$): δ 90.2 (C), 107.7 (C), 115.6 (CH), 116.6 (CH), 142.1 (C), 145.5 (C). Anal. Calcd for $C_6H_2Cl_4SN_2$ (276.0): C, 26.11; H, 0.73; N, 10.15. Found: C, 26.28; H, 0.72; N, 9.84.

Acknowledgements

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