Facile Synthesis of 6-Trichloromethylpterin and 2-Chloro-3-trichloromethylquinoxaline along with a Library of Trichloromethyl Heterocycles Using *N*-Chlorosuccinimide and Triphenyl Phosphine

Shyamaprosad Goswami,*[1] Annada C. Maity,[1] and Hoong-Kun Fun[2]
[1]*Department of Chemistry, Bengal Engineering and Science University, Shibpur, Howrah-711 103, India*
[2]*X-ray Crystallography Unit, School of Physics, University Sains Malaysia, 11800 USM, Penang, Malaysia*

(Received January 30, 2007; CL-070116)

A general synthesis of 6-trichloromethylpterin, 2-chloro-3-trichloromethylquinoxaline and 2-amino-7-trichloromethyl-1,8-naphthyridine along with a series of trichloromethyl heterocycles (**1**–**11**) has been reported in one-pot mild neutral condition in good yield. This method is compared with the usual method using phosphorus pentachloride in phosphorus oxychloride.

The halogen-substituted π-depletion heteroaromatic nuclei (e.g. pterin, quinoxaline, naphthyridine, or pyridine derivatives) are important intermediates in modern organic chemistry.[1] These are versatile key compounds in manifold synthesis of artificial receptors for molecular recognition.[2] These intermediates react with different nucleophiles such as amines to give the corresponding substituted products. 2-Amino-6-bromomethyl-4(3*H*)-pteridinone and 6-bromomethyl-2,4-pteridinediamine are the key intermediates for the synthesis of nutrient cofactor folic acid and anticancer drug methotrexate.[3] Pharmacophore based synthesis of 3-chloroquinoxaline-2-carboxamide as serotonin$_3$ (5-HT$_3$) receptor antagonist was designed and prepared from 3-chloro-2-quinoxalinylchloride.[4]

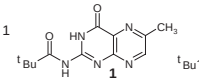
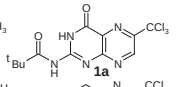
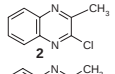
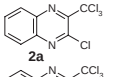
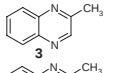
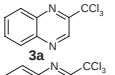
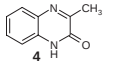
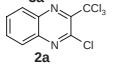
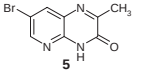
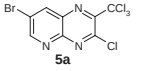
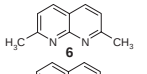
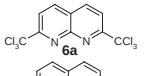
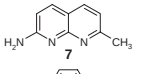
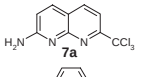
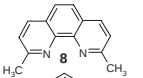
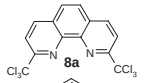
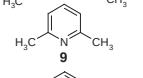
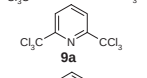
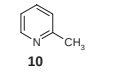
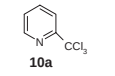
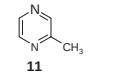
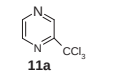
It is well known that β-methylheterocyclic compounds are chlorinated to give β-trichloromethylheterocyclic compounds using phosphorus pentachloride in phosphorus oxychloride.[5] These reagents are, however, very moisture-sensitive and also isolation of the products from phosphorus oxychloride is difficult. Thus, the development of new modes of β-methyl halogenation without using a halogenating reagent such as phosphorus oxychloride would be advantageous for many chemists. Recently, a facile halogenation of some hydroxyheterocycles using triphenylphosphine and *N*-halosuccinimide was reported.[6] We have previously reported side chain bromination in the presence or absence of water and without radical initiator under microwave.[7]

We report here a useful, straightforward, economic and efficient method for the synthesis of 6-trichloromethylpterin, 2-chloro-3-trichloromethylquinoxaline and a series of methyltrichloro-substituted heterocyclic compounds in good yield using *N*-chlorosuccinimide and triphenylphosphine in carbon tetrachloride by one-step reaction under mild and neutral conditions.

The starting material 2-amino-6-methyl-3*H*-pteridin-4-one was made by following our microwave procedure[8] and its 2-pivaloyl derivative **1** was prepared owing to extremely poor solubility of pterin in both organic and aqueous media. Thus, the ^{1}H NMR spectroscopic studies of the chloro-substituted pterins were performed with the 2-pivaloyl derivative. Similarly starting compounds 3-methyl-2(1*H*)-quinoxalinone (**4**) and 2-amino-7-methyl-1,8-naphthyridine (**7**) respectively for Entries 4 and 7 were made by reported procedures.[9,10] Lactam group in the pyrimidine ring of methylpterin **1** (Entry 1) was not converted to the chloro derivative and only the methyl group was transformed into trichloromethyl group. But the methylquinoxaline lactam **4** (Entry 4) and **5** (Entry 5) gave **2a** and **5a** where both the trimethyl and the lactam moiety were smoothly converted to the chlorinated product. A plausible mechanism is also suggested[12] for the formation of **3a** and given in the Supporting Information.[14] All the compounds made here are well characterized by spectroscopic studies (^{1}H NMR, ^{13}C NMR, and MS) as well as by comparison of melting points with authentic samples. The reaction conditions and yields are summarized in Table 1.

The experimental procedure is as follows: In a round-bottomed flask, 10 equiv. of *N*-chlorosuccinimide was added to a solution of 2 equiv. of triphenylphosphine in carbon tetra-

Table 1. Synthesis of the series of β-trichloromethyl-substituted heterocyclic compounds (**1**–**11**)

Entry	Starting material	Product	Reaction condition[a,c] NCS and PPh_3 in CCl_4	Yield[b] /%	Reference
1	 **1**	 **1a**	7 h	76	11
2	 **2**	 **2a**	6 h	84	11
3	 **3**	 **3a**	5 h	90	5b
4	 **4**	 **2a**	7 h	85	11
5	 **5**	 **5a**	6 h	75	11
6	 **6**	 **6a**	7 h	90	1d
7	 **7**	 **7a**	6 h	92	11
8	 **8**	 **8a**	7 h	95	1c
9	 **9**	 **9a**	7 h	60	11
10	 **10**	 **10a**	6 h	62	5a
11	 **11**	 **11a**	6 h	54	12

[a]Reactions were monitored by TLC analysis. [b]Yields refer to the isolated pure products after column chromatography. [c]Reaction was carried out at 80–85 °C.

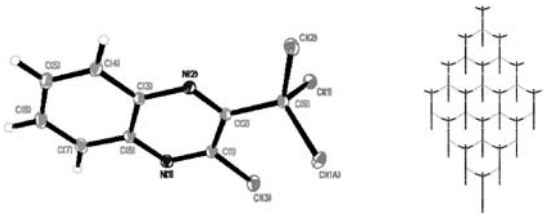


Figure 1. X-ray structure of the compound **2a**: ORTEP diagram of the compound with atom numbering scheme and supramolecular architecture within non-hydrogen inter-molecular contacts (view along *a* axis). X-ray structure of the compound **2**: (a) ORTEP diagram of the compound with atom numbering scheme. (b) Packing of molecules **2** in the crystal lattice. (c) Cl···Cl interaction of chloro and trichloromethyl groups giving helix-like conformation along *b* axis. (d) Supramolecular architecture within non-hydrogen inter-molecular contacts (view along *a* axis).

chloride (60 mL), and stirred at room temperature for 25 min. A solution of 3-methyl-2(1*H*)-quinoxalinone (**4**) (1 g, 5.25 mmol) was added to the suspension and the reaction mixture was stirred and heated under reflux for 7 h. The solution was cooled and filtered. The evaporated filtrate was washed with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. After drying over anhydrous Na_2SO_4, the solvent was removed under reduced pressure. The crude product was purified with column chromatography using silica gel and elution with 1% ethyl acetate in pet ether afforded 2-chloro-3-trichloromethylquinoxaline (**2a**) (1.47 g, 84%) as a white crystalline solid.

One important note that 2-chloro-3-dichloromethylpyrazine was prepared by chlorination of 2-chloro-3-methylpyrazine in acetic acid at 100 °C where no 2-chloro-3-trichloromethylpyrazine was formed is indicative of the steric crowding about the dichloromethyl group.[13] But in case of quinoxalines for Entries 2, 4, and 5, they formed 2-chloro-3-trichloromethylquinoxaline (**2a**) and 7-bromo-3-chloro-2-trichloromethylpyrido[2,3-*b*]pyrazine (**5a**). The structure of the compound **2a** obtained was confirmed by spectroscopic methods (IR, ^{1}H NMR, ^{13}C NMR, and MS). Final confirmation of **2a** was obtained by an X-ray crystallographic investigation (Figure 1). The molecule is relatively planar. This planar arrangement leads to a compact packing structure in parallel layers. The four molecules are present in the unit cell.

In summary, the simple and clean reaction procedure and also the work-up, use of low volumes of solvent, fast reaction rates, mild and neutral reaction conditions, good yields with no tar formation make this method for the synthesis of trichloromethyl heterocycles an attractive and useful addition to the current methodologies.

We thank DST [SR/S1/OC-13/2005], Govt. of India for financial support. ACM thanks UGC, Govt. of India for research fellowship. HKF would like to thank the Malaysian Government and University Saints Malaysia for the Scientific Advancement Grant Allocation (SAGA) grant No. 304/PFIZIK/653003/A118.

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11 6-Trichloromethyl-2-pivaloylaminopteridin-4(3*H*)-one (**1a**): Yellow crystals; mp 187–189 °C. FT-IR (Kari): 3420, 1698, 1410, 1262, 782 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 12.49 (br s, 1H, N*H*), 9.32 (s, 1H, C_7–*H*), 8.67 (br s, 1H, N*H*), 1.35 (s, 9H). MS (FAB): *m*/*z* (%): 364 (M^+, 45%). 2-Chloro-3-trichloromethylquinoxaline (**2a**): White crystals; mp 152–153 °C. FT-IR (KBr): 1536, 1478, 1335, 1277, 774 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.21 (d, 1H, $J = 7.5$ Hz), 8.11 (d, 1H, $J = 10$ Hz), 7.91 (m, 2H). MS (FAB): *m*/*z* (%): 282 (M^+, 50%). X-ray data for **2a**: $C_9H_4Cl_4N_2$: $M_r = 281.94$, orthorhombic, *Pnma* (No. 62), $a = 14.4605(2)$, $b = 6.7113(1)$, $c = 10.8469(2)$ Å, $V = 1052.68(3)$ Å^3, $Z = 4$, $D_{calcd} = 1.779$ g/cm^3. A total of 2482 unique reflections were measured at room temperature from a $0.25 \times 0.28 \times 0.36$ mm^3 colorless crystal. Atomic coordinates, bond lengths, bond angles, and thermal parameters have been deposited with the Cambridge Crystallographic Data Center (CCDC No. 295218). 2-Amino-7-trichloromethyl-1,8-naphthyridine (**7a**): White crystals; mp 202–203 °C. FT-IR (KBr): 3478, 2360, 1626, 1482, 1418, 1270, 764 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.47 (d, 1H, $J = 8.66$ Hz), 8.07 (d, 1H, $J = 8.43$ Hz), 8.01 (d, 1H, $J = 5.61$ Hz), 7.72 (d, 1H, $J = 8.41$ Hz), 5.75 (br s, 2H, NH_2). 2,6-Bis(trichloromethyl)pyridine (**9a**): White crystals; mp 115–117 °C. FT-IR (KBr): 1542, 1480, 1275, 770 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.06 (m, 3H).

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Published on the web (Advance View) March 21, 2007; doi:10.1246/cl.2007.552