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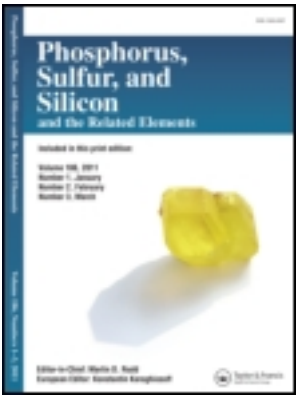

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Synthesis and Antitumor Activity Of Novel Nitrogen Mustard Derivatives Of 2, 4, 6-Trioxo-1,3,5,2-Triazaphosphorine

Shui-Ming Lu [a] , Li-Juan Mao [b] & Ye-Rong Xiong [a]

[a] Department of Chemistry , Central China Normal University , Wuhan, 430079, P. R. China , Hubei

[b] Institute of Elemento-Organic Chemistry , Nankai University , Tianjin, 300071, P.R. China

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SYNTHESIS AND ANTITUMOR ACTIVITY OF NOVEL NITROGEN MUSTARD DERIVATIVES OF 2, 4, 6-TRIOXO-1, 3, 5, 2-TRIAZAPHOSPHORINE

SHUI-MING LU[a], LI-JUAN MAO[b] and YE-RONG XIONG[a]

[a]*Department of Chemistry, Central China Normal University, Wuhan 430079, Hubei, P.R. China and* [b]*Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P.R. China*

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A series of novel nitrogen mustard derivatives of 2, 4, 6-trioxo-1, 3, 5, 2-triazaphosphorine have been synthesized by the cyclization reactions of N, N-bis(2-chloroethyl)amino phosphonyl diisocyanate with amines. The structures of the products were confirmed by ^{1}H NMR, IR, MS and elemental analysis. The preliminary bioassay indicated that some of the compounds significantly inhibited the growth of Leukemia L1210 cell in vitro.

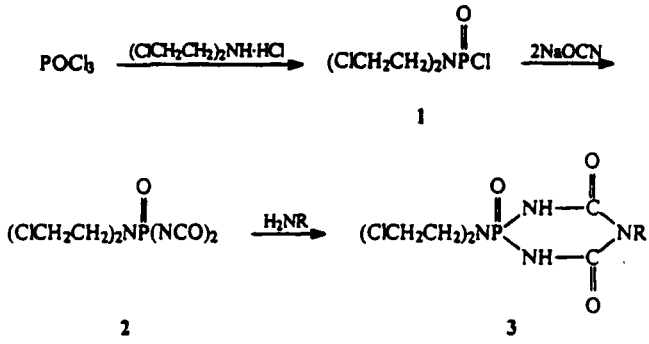
Keywords: Triazaphosphorine; phase transfer catalysis; synthesis; antitumor activity

INTRODUCTION

The synthesis and antitumor activity of the phosphoryl nitrogen mustard derivatives are well documented.[1-3] Some are widely applied in cancer chemotherapy, such as Endoxan and Holoxan, but the by-effects of these drugs on marrow cells and urinary system somewhat limit their clinical use.[4] Therefore, attempts to modify the structures of the nitrogen mustard derivatives of cyclophamide for an enhancement of their chemotherapeutic properties were made.

As part of an ongoing programme and interest in the development of antitumor compounds with high activity and low toxicity, we herein designed and synthesized a series of novel nitrogen mustard derivatives of

2,4,6-trioxo-1,3,5,2-triazaphosphorine **3** by the cyclization reactions of N, N-bis(2-chloroethyl)amino phosphoryl diisocyanate (**2**) with amines. The synthetic route is shown in Scheme 1.



R = C_6H_5, *p*-ClC_6H_4, *m*-ClC_6H_4, *o*-ClC_6H_4, *p*-MeC_6H_4, *m*-MeC_6H_4, *o*-MeC_6H_4, *p*-BrC_6H_4, *m*-BrC_6H_4, *o*-BrC_6H_4, *p*-$NO_2C_6H_4$, *m*-$NO_2C_6H_4$, *n*-Pr, *i*-Pr

SCHEME 1

DISCUSSION AND RESULTS

1. Synthesis of the Intermediate 2

The phosphoryl diisocyanates are important intermediates in the synthesis of some biological active compounds,[5–6] but the preparative procedures in the literature are not satisfactory due to drastic reaction conditions and difficulty accessible starting materials.[7–9] Here we provide a convenient and efficient one-step synthesis of compound **2**. N, N-bis(2-chloroethyl)amino phosphoryl dichloride (**1**) was allowed to react with sodium cyanate in acetonitrile under the condition of solid-liquid phase transfer catalysis using PEG-600 as the catalyst to afford the intermediate **2** in 66.6 % yield. In this reaction, the phase transfer catalyst played an important role, in the absence of the catalyst, changes of reaction conditions, i.e., temperature, time and solvent of reaction, could not give **2**, but when PEG-600 was used as a phase transfer catalyst, the reaction went on smoothly under reflux.

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2. The Cyclization Reactions of 2 with Amines

The cyclization reactions of N, N-bis(2-chloroethyl)amino phosphoryl diisocyanate (2) with aromatic amines in toluene gave desired products **3** in satisfactory yields. The results are summarized in Table I.

TABLE I Physical constants and analytical data of compounds **3**

No.	*R*	*Yield (%)*	*m.p. (°C)*	*Elemental analysis/Found (Calcd.)*		
				C	*H*	*N*
3a	C_6H_5	70. 5	205–206	39. 38(39. 46)	4. 06(4. 11)	15. 29(15. 35)
3b	*p*-ClC_6H_4	68. 7	212–213	35. 89(36. 06)	3. 47(3. 51)	13. 94(14. 02)
3c	*m*-ClC_6H_4	60. 3	208–209	35. 91(36. 06)	3. 45(3. 51)	13. 95(14. 02)
3d	*o*-ClC_6H_4	40. 8	198–199	36. 01(36. 06)	3. 47(3. 51)	14. 05(14. 02)
3e	*p*-MeC_6H_4	75. 2	201–202	41. 05(41. 17)	4. 42(4. 49)	14. 78(14. 78)
3f	*m*-MeC_6H_4	65. 8	215–216	41. 09(41. 17)	4. 47(4. 49)	14. 71(14. 78)
3g	*o*-MeC_6H_4	50. 4	203–204	41. 00(41. 17)	4. 45(4. 49)	14. 77(14. 78)
3h	*p*-BrC_6H_4	65. 8	189–190	32. 21(32. 44)	3. 11(3. 15)	12. 59(12. 62)
3i	*m*-BrC_6H_4	54. 6	201–202	32. 27(32. 44)	3. 13(3. 15)	12. 53(12. 62)
3j	*o*-BrC_6H_4	38. 8	193–194	32. 33(32. 44)	3. 10(3. 15)	12. 55(12. 62)
3k	*p*-$NO_2C_6H_4$	50. 5	221–222	34. 98(35. 13)	3. 40(3. 42)	17. 01(17. 08)
3l	*m*-$NO_2C_6H_4$	42. 8	210–211	35. 01(35. 13)	3. 39(3. 42)	16. 99(17. 08)
3m	*n*-Pr	11. 1	137–138	32. 47(32. 64)	5. 11(5. 14)	16. 85(16. 92)
3n	*i*-Pr	10. 2	123–124	32. 54(32. 64)	5. 09(5. 14)	16. 87(16. 92)

We found that the cyclization reaction was affected remarkably by electronic and steric effects of the substituent in the benzene ring of aromatic amine. When an electron-donating group was at the *para-* or *meta-* position of the aniline, the reaction went on easily. On the other hand, when an electron-donating group was at *ortho*-position or an electron-withdrawing group was at the *para-* or *meta*-position, the cyclization was slower and the yield was lower. Unfortunately, when aniline bearing electron-withdrawing group at the *ortho-* position was used, the reaction failed to give any product.

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TABLE II ^1H NMR, IR and MS data of compounds 3

No.	*^1H NMR (δ, ppm)*	*IR (cm^{-1})*	*MS (M^+, m/z)*
3a	3. 42–3. 63 (m, 8H, $2ClCH_2CH_2$), 7. 25-7. 51 (m, 5H, C_6H_5)	3350,2980,1655,1450 1230,1175,1110,985	365
3b	3. 39–3. 65 (m, 8H, $2ClCH_2CH_2$), 7. 27-7. 61 (m, 4H, C_6H_4)	3405,2955,1660,1435 1250,1180,1110,980	399
3c	3. 45–3. 68 (m, 8H, $2ClCH_2CH_2$), 7. 25-7. 60 (m, 4H, C_6H_4)	3400,2940,1660,1450 1230,1180,1110,965	399
3d	3. 36–3. 69 (m, 8H, $2ClCH_2CH_2$), 7. 21-7. 57 (m, 4H, C_6H_4)	3365,2960,1655,1455 1240,1170,1080,955	399
3e	2. 31 (s, 3H, CH_3), 3.35–3.71 (m, 8H, $2ClCH_2CH_2$), 7. 31–7. 57 (m, 4H, C_6H_4)	3380,2955,1660,1450 1250,1185,1095,960	379
3f	2. 30 (s, 3H, CH_3), 3. 37–3. 69 (m, 8H, $2ClCH_2CH_2$), 7. 22–7. 64 (m, 4H, C_6H_4)	3400,2985,1650,1485 1255,1170,1100,950	379
3g	2. 34 (s, 3H, CH_3), 3. 41–3. 72 (m, 8H, $2ClCH_2CH_2$), 7.22–7.71 (m, 4H, C_6H_4)	3360,2980,1655,1445 1230,1170,1085,965	379
3h	3. 41–3. 69 (m, 8H, $2ClCH_2CH_2$), 7. 39-7. 63 (m, 4H, C_6H_4)	3380,2975,1660,1485 1250,1180,1090,945	444
3i	3.44 3. 67 (m, 8H, $2ClCH_2CH_2$), 7. 21-7. 55 (m, 4H, C_6H_4)	3400,2905,1655,1430 1245,1165,1060,970	444
3j	3. 40–3. 65 (m, 8H, $2ClCH_2CH_2$), 7. 34-7. 66 (m, 4H, C_6H_4)	3395,2950,1655,1450 1250,1150,1085,955	444
3k	3. 42–3. 72 (m, 8H, $2ClCH_2CH_2$), 7. 32-7. 89 (m, 4H, C_6H_4)	3360,2960,1660,1475 1245,1175,1105,960	410
3l	3. 38–3. 75 (m, 8H, $2ClCH_2CH_2$), 7. 35-8. 05 (m, 4H, C_6H_4)	3400,2985,1660,1485 1250,1165,1090,975	410
3m	1. 06 (t, 3H, CH_3), 1. 91–2. 48 (m, 4H, $2CH_2$), 3. 35–3. 69 (m, 8H, $2ClCH_2CH_2$)	3370, 2945,1660,1460 1235,1170,1100,950	331
3n	1. 23 (m, 6H, $2CH_3$), 3. 32–3. 72 (m, 9H, $2ClCH_2CH_2$, CH)	3400,2970,1655,1485 1250,1150,1070,950	331

TABLE III The antitumor activity of compounds 3[a]

No.	***3a***	***3b***	***3c***	***3d***	***3e***	***3f***	***3g***
Drug amount (μg/mL)	0.753	0.306	0.356	0.413	0.533	0.612	0.634
Inhibition rate (IC50)	50	50	50	50	50	50	50
No.	**3h**	**3i**	**3j**	**3k**	**31**	**3m**	**3n**
Drug amount (μg/mL)	0.833	0.875	0.911	0.951	0.989	0.553	0.601
Inhibition rate (IC50)	50	50	50	50	50	50	50

[a]Cancel cell is L1210 and time is 72h

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Besides aromatic amines, aliphatic amines can also react with **2** under the same conditions, but the yields of products **3** were very low (e.g. **3m** and **3n**). Due to their higher reactivity, more by-products might be produced so that the yields were significantly reduced.

3. The Structures of Compounds 3

The structures of all new compounds **3** prepared were confirmed by ^1H NMR, IR, MS and elemental analysis. The results are listed in Table I and Table II.

^1H NMR spectra of the compounds **3** have been determined in deuteroacetone on a 200MHz NMR instrument. The methylene protons of the nitrogen mustard appeared as a set of characteristic complex absorption bands in the range of δ 3.3–3. 8ppm and the protons of the phenyl groups displayed multiplet peaks at δ 7.2–8. 1ppm, but the proton signals in the phosphorus heterocycle was not observed. For IR spectra, the normal stretching absorption bands indicated the existence of the groups NH (3350–3400cm^{-1}), C=O (1650–1660cm^{-1}) and P=O (1230–1250cm^{-1}). The EI-MS spectra of compounds **3** revealed that the molecular ion peaks and fragmentation peaks were consistent with their structures.

4. Antitumor Activity of Compounds 3

The preliminary antitumor tests in vitro were carried out by the MTT methods. The results which are given in Table III indicated that some of compounds **3** had a high inhibitory effect of the growth of Leukemia L1210 cells.

EXPERIMENTAL

Melting points were uncorrected. Elemental analyses were carried on a PE-2400 instrument. ^1H NMR spectra were recorded in deuteroacetone on a Varian XL-200 spectrometer and TMS was used as an internal standard. IR spectra were measured on a Shimadzu-40 spectrometer. Mass spectra were taken on a HP 5988A spectrometer. Column chromatography was

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performed on silica gel H (10–40μ, Haiyang Chemical Factory of Qingdao).

The reagents and solvents were available commercially and purified according to conventional methods.

N, N-Bis(2-chloroethyl)amino Phosphoryl Dichloride (1)

A mixture of dry N, N-bis(2-chloroethyl)amine hydrochloride (30. 0g, 0.17 mol) and phosphoryl chloride (78 mL, 0.81 mol) was heated at 120–140°C for 14h. After removal of excess phosphoryl chloride under reduced pressure, the crude product was recrystallized from acetone-petroleum ether (60–90°C) to give compound **1** (36.0 g, 82.6 %), m.p. 53–54°C (Lit[10]: yield 80 %, m.p. 53 - 56°C).

N, N-Bis(2-chloroethyl)amino Phosphoryl Diisocyanate (2)

To a solution of N, N-bis(2-chloroethyl)amino phosphoryl dichloride (**1**) (2.0 g, 7.7 mmol) and PEG-600 (0.5 g) in dry acetonitrile (40 mL) was added portionwise sodium cyanate (1.5 g, 23 mmol) in 30 min with stirring, the mixture was refluxed under $N_2$for another 6 h. After filtration, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with a mixture of chloroform, diethyl ether and petroleum ether (60–90°C) (1:1:3) as the eluent to give colorless crystals **2** (1.4 g, 66.6 %), m.p. 76–77°C. Anal. Calcd. for $C_6H_8Cl_2N_3O_3P$: C, 26.48; H, 2.49; N, 15.45. Found: C, 26.31; H, 2.90; N, 15. 38. IR (KBr): ν 2950, 2210, 1250, 1180, 1095, 985cm^{-1}. ^{1}H NMR (CD_3COCD_3): δ 3.35–3.71 (m, 8H, $2CH_2CH_2$). ^{31}P NMR (CD_3COCD_3): δ 20.12. MS (%): m/z 273 (M^++2, 8), 271 (M^+, 12), 222 (100).

General Procedure of the Cyclization Reactions of 2 with Amines

To a solution of N, N-bis(2-chloroethyl)amino phosphoryl diisocyanate (**2**) (1.0 g, 3.7 mmol) in anhydrous toluene (60 mL) was added dropwise amine (3.7 mmol) in anhydrous toluene (20 mL) on ice-salt bath. The mixture was first stirred at ambient temperature for 2 h and 60°C for 4 h, then refluxed for an additional 6 h. After cooling, the precipitate was collected by filtration and recrystallized from acetone-diethyl ether to give a white

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or yellow solid as product **3**. The physical and spectral data are listed in Table I and Table II.

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