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A new reaction of *N*-aryl-2-pyrimidinamines with triphosgene

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Abstract—A new reaction of *N*-aryl-2-pyrimidinamines with triphosgene to afford *N*-aryl-*N*-(2-pyrimidinyl)-2-pyrimidinamine is described.

In an ongoing program we needed to synthesize the symmetrical urea **3a** (Scheme 1). We reasoned that **3a** can be easily prepared by a reaction of *N*-phenyl-2-pyrimidinamine (**1a**)[1] with 0.2 equiv of bis(trichloromethyl) carbonate (triphosgene), which is a less hazardous substitute for phosgene.[2–4] These conditions, however, led to the unexpected *N*-phenyl-*N*-(2-pyrimidinyl)-2-pyrimidinamine (**2a**). In this Letter, we report this new deamination-self amination reaction of *N*-aryl-2-pyrimidinamines with triphosgene. Such a reaction of *N*-aryl-2-pyrimidinamines with triphosgene has not been reported to the best of our knowledge.[5,6]

Treatment[7] of *N*-phenyl-2-pyrimidinamine (**1a**) with 0.2 equiv of triphosgene in refluxing toluene yielded the desired symmetrical urea **3a** in only 1.5% yield (3% of theory; Table 1, entry 1). *N*-Phenyl-*N*-(2-pyrimidinyl)-2-pyrimidinamine (**2a**) was isolated as the major product in 36% yield (72% of theory). The structure of **2a** was assigned based on spectroscopic data.[8] This deamination-self amination reaction of **1a** with triphosgene represents a novel route to **2a**. To examine the scope, we next investigated this new reaction with several substrates. The results are listed in Table 1. Reaction of **1b**, with an electron-donating group in the phenyl ring, afforded the desired product **2b** in 43% yield (86% of theory; entry 2). No symmetrical urea **3b** was observed in this reaction. Introduction of an electron-withdrawing substituent in the phenyl ring (**1c**), gave 31% yield (62% of theory) of the desired product **2c** (entry 3). In this case the symmetrical urea **3c** was produced in 8% yield (16% of theory). A phenyl substituent in the pyrimidine ring (**1d**) also afforded the expected product **2d** in 43.5% yield (87% of theory; entry 4). Reaction of *N*-butyl-2-pyrimidinamine (**1e**) with triphosgene also afforded the deaminated-self aminated product **2e** in 24.5% yield (49% of theory) along with 10% (20% of theory) of the symmetrical urea **3e** (entry 5). Removal of one of the nitrogen atoms from the pyrimidine ring, as in *N*-phenyl-2-pyridinamine (**1f**), gave mainly the unreacted starting material. Only 5% yield (10% of theory; entry 6) of the desired product **2f** was obtained. To the best of our knowledge this method represents the first synthesis of *N*-aryl-*N*-(2-pyrimidinyl)-2-pyrimidinamines.

A plausible mechanism for the deamination-self amination reaction of *N*-aryl-2-pyrimidinamines with triphosgene is illustrated in Scheme 2. The initially formed imidoyl chloride intermediate (**A**) from the reaction of *N*-aryl-2-pyrimidinamines (**1**) with triphosgene, could undergo a nucleophilic displacement at 2-position by another molecule of **1** to afford the deaminated-self aminated product (**2**). Intermediate (**A**) could also undergo a C–N bond cleavage reaction to afford intermediate **B**, which then reacts with another molecule of **1** to yield **2**. Intermediate **B** could also lead to the formation of 2-chloropyrimidine that can then react with another molecule of **1** to afford **2**. An HPLC analysis of the reaction mixture at intervals did not indicate the presence of 2-chloropyrimidine. Additionally, treatment of

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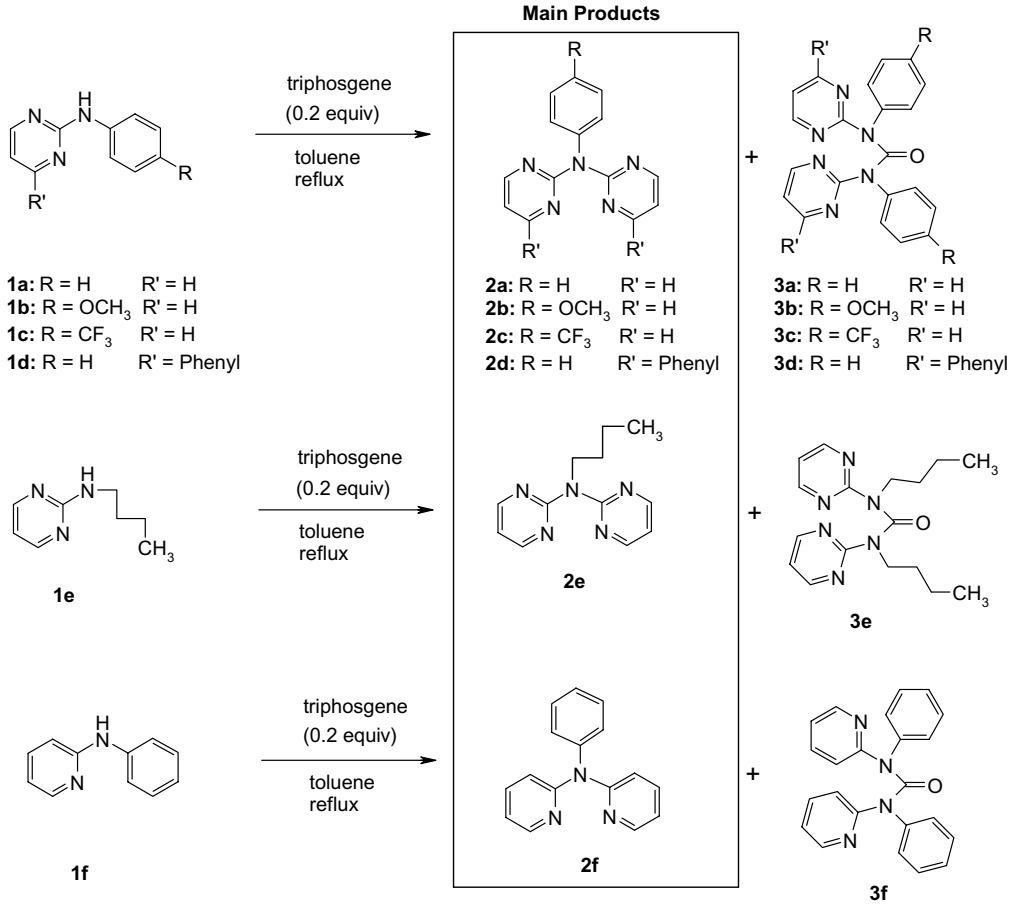


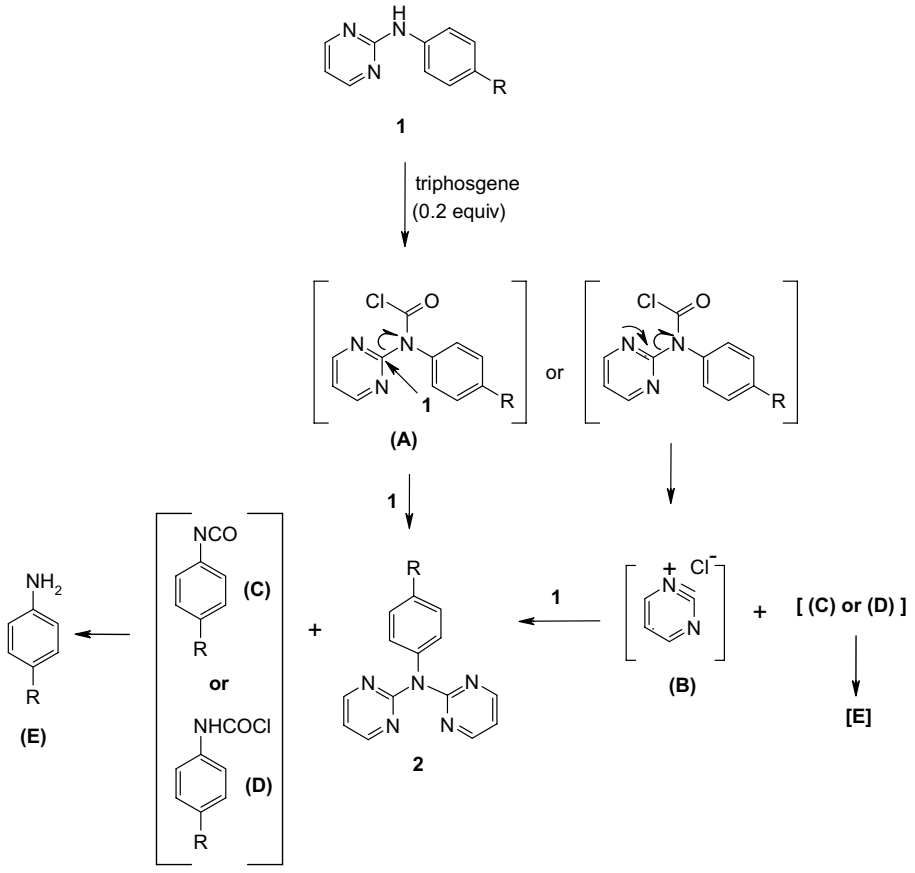
Scheme 1.

Table 1. Reaction of *N*-aryl-2-pyrimidinamines with triphosgene

Entry	Starting material	R	R′	Product (s)	% Isolated yield (% of theory)
1	**1a**	H	H	**2a** **3a**	36 (72) 1.5 (3)
2	**1b**	OCH_3	H	**2b** **3b**	43 (86) Not detected
3	**1c**	CF_3	H	**2c** **3c**	31 (62) 8 (16)
4	**1d**	H	Phenyl	**2d** **3d**	43.5 (87) Not detected
5	**1e**	—	—	**2e** **3e**	24.5 (49) 10 (20)
6	**1f**	—	—	**2f** **3f**	5 (10) Not detected

2-chloropyrimidine with **1a** in refluxing toluene did not lead to the formation of **2a**. These results suggest that 2-chloropyrimidine is not an intermediate in this reaction. An LC–MS analysis of the reaction mixture from **1a** indicated the formation of intermediate (**A**), product **2a**, and aniline (**E**). Aniline (**E**) could be formed either via phenyl isocyanate (**C**) or imidoyl chloride (**D**), neither of which was detected by LC–MS. Such a deamination-self amination reaction was not observed by a reaction of **1b** with *p*-nitrophenyl chloroformate.

In summary, a new deamination-self amination reaction of *N*-aryl-2-pyrimidinamines with triphosgene to afford *N*-aryl-*N*-(2-pyrimidinyl)-2-pyrimidinamine is described.



Scheme 2.

References and notes

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7. *Typical procedure:* A mixture of **1a**–**f** (5.0 mmol), triphosgene (0.83 mmol), and toluene (20.0 mL) was refluxed (110 °C internal temperature) for 8 h. A second portion of triphosgene (0.166 mmol) was added and the refluxing was continued for an additional 16 h. The reaction mixture was cooled to room temperature and basified with 2 N sodium hydroxide (14.0 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (20.0 mL). The combined organic layers were dried and concentrated. The crude material was purified by silica gel chromatography.
8. Compound **2a**: mp 164–166 °C; ^{1}H NMR (DMSO-d_6, δ) 7.1–7.25 (m, 5H), 7.37 (t, 2H, $J = 4.7$ Hz), 8.61 (d, 4H, $J = 4.7$ Hz); ^{13}C NMR (DMSO-d_6, δ) 117.3, 125.9, 127.3, 129.4, 143.7, 158.8, 162.7: MS (ESI) 250.2 (MH^+). Compound **2b**: mp 129–130 °C; ^{1}H NMR (DMSO-d_6, δ) 3.76 (s, 3H), 6.93 (dd, 2H, $J = 6.8$ and 2.3 Hz), 7.06 (dd, 2H, $J = 6.8$ and 2.3 Hz), 7.13 (t, 2H, $J = 4.7$ Hz), 8.58 (d, 4H, $J = 4.7$ Hz); ^{13}C NMR (DMSO-d_6, δ) 55.6, 114.7, 116.6, 129.1, 136.4, 157.7, 158.7, 162.8; MS (ESI) 280.2 (MH^+). Compound **2c**: mp 184–186 °C; ^{1}H NMR (CD_3OD, δ) 7.20 (t, 2H, $J = 4.9$ Hz), 7.33 (d, 2H, $J = 8.4$ Hz), 7.68 (d, 2H, $J = 8.4$ Hz), 8.60 (d, 4H, $J = 4.9$ Hz); ^{13}C NMR (DMSO-d_6, δ) 117.7, 124.6 (q, $J_{C-F} = 270.0$ Hz), 125.1, 125.5, 126.4, 127.0, 130.0, 147.3, 159.0, 162.3; MS (ESI) 318.2 (MH^+). Compound **2d**: mp 140–142 °C; ^{1}H NMR (DMSO-d_6, δ) 7.26–7.28 (m, 3H), 7.39–7.50 (m, 8H), 7.77 (d, 2H, $J = 5.3$ Hz), 7.99–8.02 (m, 4H), 8.70 (d, 2H, $J = 5.3$ Hz); ^{13}C NMR (DMSO-d_6, δ) 112.3, 126.0, 127.4, 129.3, 131.5, 136.3, 143.6, 159.6, 162.9, 164.3; MS (ESI) 402.3 (MH^+). Compound **2e**: oil; ^{1}H NMR (CD_3OD, δ) 0.91 (t, 3H, $J = 7.4$ Hz), 1.21–1.41 (m, 2H), 1.63–1.73 (m, 2H), 4.29 (t, 2H, $J = 7.5$ Hz), 7.06 (t, 2H, $J = 4.9$ Hz), 8.57 (d, 4H, $J = 4.9$ Hz); ^{13}C NMR (CD_3OD, δ) 14.6, 21.5, 25.8, 32.1, 117.0, 159.9, 163.5; MS (ESI) 230.2 (MH^+). Compound **2f**: mp 83–85 °C; ^{1}H NMR (CD_3OD, δ) 6.94–6.97 (m, 2H), 7.02–7.06 (m, 2H), 7.11–7.14 (m, 2H), 7.20–7.25 (m, 1H), 7.32–7.41 (m, 2H), 7.60–7.72 (m, 2H), 8.13–8.21 (m, 2H); ^{13}C NMR (CD_3OD, δ) 119.3, 120.4, 127.4, 128.6, 131.4, 140.2, 146.5, 149.4, 159.8; ^{1}H NMR (CD_3OD, δ). Compound **3a**: ^{1}H NMR (DMSO-d_6, δ) 7.10–7.15 (m, 6H), 7.16–7.23 (m, 2H), 7.26–7.32 (m, 4H), 8.54 (d, 4H, $J = 4.9$ Hz); MS (ESI) 369.3 (MH^+). Compound **3c**: mp 215–218 °C; ^{1}H NMR (CD_3OD, δ) 7.14 (t, 2H, $J = 4.9$ Hz), 7.38 (d, 4H, $J = 8.3$ Hz), 7.60 (d, 4H, $J = 8.5$ Hz), 8.54 (d, 4H, $J = 4.9$ Hz); MS (ESI) 505.1 (MH^+). Compound **3e**: oil; ^{1}H NMR (CD_3OD, δ) 0.94 (t, 6H, $J = 7.4$ Hz), 1.36–1.43 (m, 4H), 1.65–1.79 (m, 4H), 4.07 (t, 4H, $J = 7.3$ Hz), 6.75 (t, 2H, $J = 4.9$ Hz), 8.26 (d, 4H, $J = 4.9$ Hz); MS (ESI) 329.1 (MH^+).