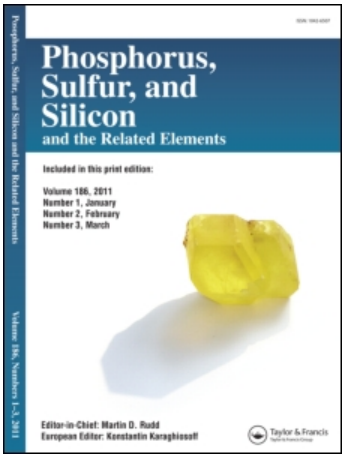

Phosphorus, Sulfur, and Silicon and the Related Elements

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A Convenient Synthesis of 1,2,4-Triazolo-1,3,5-triazin-4-ones and 1,2,4-Triazolo-1,3,5-triazin-4-thiones

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The imidates derived from 3-aminotriazole 1 react with isocyanates and isothiocyanates to give corresponding 1,2,4-triazolo-1,3,5-triazin-4-ones and 1,2,4-triazolo-1,3,5-triazin-4-thiones in a 60–75% overall yield. If the condensation is realized at r.t., then the intermediate 2 can be isolated.

Keywords 1,2,4-triazolo-1,3,5-triazin-4-ones; 1,2,4-triazolo-1,3,5-triazin-4-thiones; imidates; isocyanates; isothiocyanates

INTRODUCTION

It is perhaps unnecessary to emphasize the importance of the 1,2,4-triazole nucleus and its derivatives in organic chemistry. The triazolotriazines are an important class of heterocyclic compounds. Its derivatives have been claimed to be effective as potent antagonists for the human adenosine A_{2B} receptor with high affinity,[1–7] while some have shown potent antitumor and pharmacological activity.[8–11]

Conventionally, triazolotriazines are synthesized by many methods.[7–11] Great interest has been focused on the synthesis of theses compounds due to the wide variety of their uses. We report in this article a series of triazolotriazines prepared by the addition of imidates type **1** to isocyanates and isothiocyanates in THF at r.t. (Scheme 1).

The structure of compound **2** was deduced from their IR and ^{1}H spectra.

The IR spectrum of **2** revealed bands at $\nu = 3460$–3310 (NH─C═O, NHC═S) and $\nu_{C=N} = 1630$ cm^{-1}.

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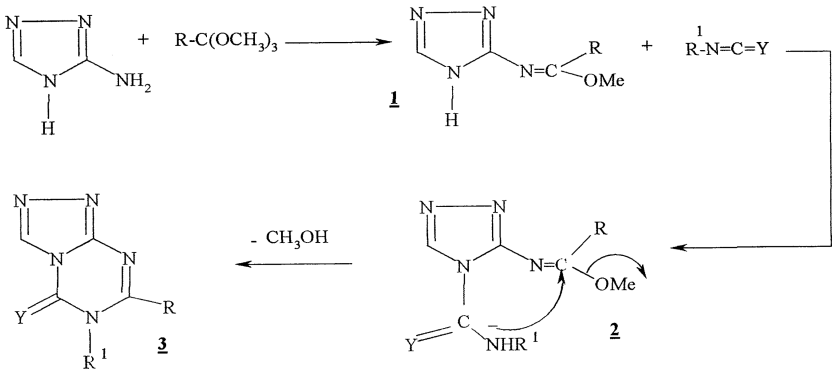

	R	R^1	Y
2a	Me	Ph	O
2b	Et	Ph	O
2c	Me	Ph	S

3	R	R1	Y
3a	Me	Ph	O
3b	Et	Ph	O
3c	Me	Ph-CH_2	O
3d	Et	Ph-CH_2	O
3e	Me	Ph	S
3f	Et	Ph	S
3g	Me	Ph-CH_2	S
3h	Et	Ph-CH_2	S

SCHEME 1

The ^{1}H NMR spectra of **2** exhibited one single sharp line arising from NH ($\delta = 10.3$ ppm) along with characteristic singlets and multiplets for the methoxy, ethoxy, ethyl, and phenyl group.

The structures of compounds **3** have been unambiguously characterized from their IR, ^{1}H, and ^{13}C spectra.

The ^{1}H NMR spectra of **3** presents the absence of the sharp line of NH and the disappearance of an ethoxy or methoxy peak with usul signals of CH_2—N, CH_3,CH_2—CH_3, and Ar-H.

The formation of compound **3** was confirmed by the IR spectra showing the disappearance of the NH band but a strong band in the region 1160–1200 cm^{-1} assigned to C=S, a strong band in the region 1720–1740 cm^{-1} assigned to the carbonyl group, and another band in the region 1620 cm^{-1} assigned to C=N.

The ^{1}H and ^{13}C NMR were used to distinguish structure **2** from the triazolo-triazine **3**.

The attack of the central carbon atom of the isocyanate or isothiocyanate by the nitrogen atom of imidate **1** forms intermediate **2**. The

latter undergoes intramolecular nucleophilic cyclization to give the derivatives triazolotriazines **3**.

EXPERIMENTAL

IR spectra were run in a $CHCI_3$ solution on a Perkin Elmer Paragon 1000 PC spectrometer.

^1H and ^{13}C NMR spectra were recorded with $CDCI_3$ as a solvent containing TMS on a Brücker 300 spectrometer. The chemical shifts are reported in ppm relative to TMS. For the ^1H NMR, the multiplicities of signals are indicated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet.

Melting points were obtained using a Büchi melting point apparatus.

Synthesis of Imidates Type 1

Imidates type **1** were prepared by the reaction of 3-amino-1,2,4-triazole with orthoester according to a published procedure.[12–14] All other reagents were commercially available (Aldrich Chemical); THF was dried and distilled over Na/naphthalene before use.

1a: Yield = 75%, m.p. = 85°C, IR ($CHCI_3$, ν (cm^{-1})): $\nu_{NH} = 3460$, $\nu_{C=N} = 1660$, ^1H NMR ($CDCI_3$): 10.1 (1,1H); 7.9 (s, 1H), 2.2 (s, 3H), 3.9(s, 3H).

1b: Yield = 72%, m.p. = 90°C, IR ($CHCI_3$, $\nu(cm^{-1})$) = $\nu_{NH} = 3460$, $\nu_{C=N} = 1660$, ^1H NMR ($CDCI_3$): 9.8 (I, 1H); 7.9 (s, 1H), 2.2 (s, 3H), 4.3 (q, 2H), 1.4 (t, 3H).

1c: Yield = 76%, m.p. = 50°C, IR ($CHCI_3$, $\nu(cm^{-1})$) $\nu_{NH} = 3460$, $\nu_{C=N} = 1670$, ^1H NMR ($CDCI_3$): 8.2 (s, 1H); 7.8 (s, 1H), 2.5 (q, 2H), 4.3 (q, 2H), 4.3 (t, 3H), 1.3 (t, 3H).

1d: Yield = 90%, m.p. = 170°C, IR (KBr, $\nu(cm^{-1})$): $\nu_{NH} = 3300$, $\nu_{C=N} = 1650$, ^1H NMR (CD_3OD): 7.3 (s, 1H); 7.8 (s, 1H), 7.3 (s, 5H), 4.5 (q, 2H), 1.5 (t, 3H).

1e: Yield = 85%, m.p. = 167°C, IR (KBr, $\nu(cm^{-1})$): $\nu_{NH} = 3300$, $\nu_{C=N} = 1650$, ^1H NMR (DMSO d_6): 7.3 (s, 1H); 7.8 (s, 1H), 7.3 (s, 5H), 4. (s, 3H).

General Procedure for the Preparation of 1,2,4-Triazolo-1,3,5-triazin-4-ones and 1,2,4-Triazolo-1,3,5-triazin-4-thiones Type 3

To a solution of imidate **1** (10 mmol) in dry THF was added isocyanate or isothiocyanate (10 mmol). The mixture was left at r.t. until a solid of **3** precipitated (7–10 days). The product **2** obtained and sometimes

was refluxed for 3 h in chlorobenzene; the solid product was filtered and purified by recrystallization from methanol.

2a: Yield = 80%, m.p. = 190°C, IR ($CHCl_3$, $\nu(cm^{-1})$): $\nu_{NH} = 3450$, $\nu_{C=N} = 1650$, $\nu_{C=O} = 1720$, ^1H NMR ($CDCl_3$): 9.15 (s, 1H); 10.3 (1, 1H), 7.2–7.9 (mu, 5H), 3.85 (s, 3H), 2.2(s, 3H).

2b: Yield = 85%, m.p. = 200°C, IR ($CHCl_3$, $\nu(cm^{-1})$): $\nu_{NH} = 3450$, $\nu_{C=N} = 1650$, $\nu_{C=O} = 1720$, ^1H NMR ($CDCl_3$): 9.15 (s, 1H); 10.3 (1, 1H), 7.2–7.9 (mu, 5H), 3.85 (s, 3H), 2.5 (q, 2H), 1.3 (t, 3H).

2c: Yield = 82%, m.p. = 92°C, IR ($CHCl_3$, $\nu(cm^{-1})$): $\nu_{NH} = 3310$, $\nu_{C=N} = 1650$, $\nu_{C=S} = 1720$, ^1H NMR ($CDCl_3$): 9.15 (s, 1H); 10.3 (1, 1H), 7.5 (mu, 5H), 3.85 (s, 3H), 2.2 (s, 3H).

3a: Yield = 60%, m.p. = 190°C, IR ($CHCl_3$, $\nu(cm^{-1})$): $\nu_{C=N} = 1610$, $\nu_{C=O} = 1710$, ^1H NMR ($CDCl_3$): 2.4(s, 3H); 7–7.4(mu, 5H); 10(s, 1H), ^{13}C NMR ($CDCl_3$): 15.7; 124; 138; 129; 131; 141.5; 148; 159.5; 160.

3b: Yield = 67%, m.p. = 160°C, IR ($CHCl_3$, $\nu(cm^{-1})$): $\nu_{C=N} = 1615$, $\nu_{C=O} = 1710$, ^1H NMR ($CDCl_3$): 1.2(t, 3H); 2.4(s, 3H); 7–7.4(mu, 5H); 10(s, 1H). ^{13}C NMR ($CDCl_3$): 10.5; 30; 124; 129.5; 138; 140; 141.2; 147; 157.5; 160.

3c: Yield = 63%, m.p. = 210°C, IR ($CHCl_3$, $\nu(cm^{-1})$): = $\nu_{C=N} = 1610$, $\nu_{C=O} = 1710$, ^1H NMR ($CDCl_3$): 2.2(s, 3H); 4.6(1, 2H); 7.2–7.4(mu, 5H); 10 (s, 1H). ^{13}C NMR ($CDCl_3$): 17.5; 46; 128; 129; 130.7; 136.4; 141.2; 151; 157.5; 161.

Analysis calcd: C = 55.6; H = 4.5; N = 29%; Found: C = 55.4; H = 4.3; N = 28.7%.

3d: Yield = 65%, m.p. = 172°C, IR ($CHCl_3$, $\nu(cm^{-1})$): $\nu_{C=N} = 1610$, $\nu_{C=O} = 1710$, ^1H NMR ($CDCl_3$): 2.2(s, 3H); 4.6(1, 2H); 7.2–7.4(mu, 5H); 10(s, 1H). ^{13}C NMR ($CDCl_3$): 17.5; 46; 128; 129; 130.7; 136.4; 141.2; 151; 157.5; 161.

3e: Yield = 65%, m.p. = 105°C, IR ($CHCl_3$, $\nu(cm^{-1})$): $\nu_{C=N} = 1610$, $\nu_{C=S} = 1190$, ^1H NMR ($CDCl_3$): 2.2(s, 3H); 7–7.4(mu, 5H); 8.3(s, 1H). ^{13}C NMR ($CDCl_3$): 14.5; 124; 131; 132;141.2; 145 154; 156.5; 181.

3f: Yield = 68%, m.p. = 115°C, IR ($CHCl_3$, $\nu(cm^{-1})$): $\nu_{C=N} = 1610$, $\nu_{C=S} = 1200$, ^1H NMR ($CDCl_3$): 1.2(t, 3H); 2.7(q, 2H); 7–7.7 (mu, 5H); 8.4(s, 1H). ^{13}C NMR ($CDCl_3$): 11.5; 27; 123.5; 131; 132.6; 140.7; 147; 156; 157.5; 184.

3g: Yield = 70%, m.p. = 200°C, IR ($CHCl_3$, $\nu(cm^{-1})$): $\nu_{C=N} = 1610$, $\nu_{C=S} = 1190$, ^1H NMR ($CDCl_3$): 2.2(s, 3H); 5.6(1, 2H); 7–7.7 (mu, 5H); 8.5 (s, 1H). ^{13}C NMR ($CDCl_3$): 17.5; 55; 128; 129; 129.7; 131.4; 140; 156; 159.5; 189.

3h: Yield = 75%, m.p. = 180°C, IR ($CHCl_3$, $\nu(cm^{-1})$): $\nu_{C=N} = 1610$, $\nu_{C=S} = 1190$, ^1H NMR ($CDCl_3$): 1.2 (t, 3H); 5.6(1, 2H); 2.5(q, 2H); 7–7.7 (mu, 5H); 8 (s, 1H). ^{13}C NMR ($CDCl_3$): 11.5; 27; 55; 128; 129; 130; 140.7; 141.4; 155; 159.5; 189.

Analysis calcd.: C = 59.6, H = 4.8; N = 25.7%. Found: C = 59.2; H = 4.7; N = 25.4%.

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