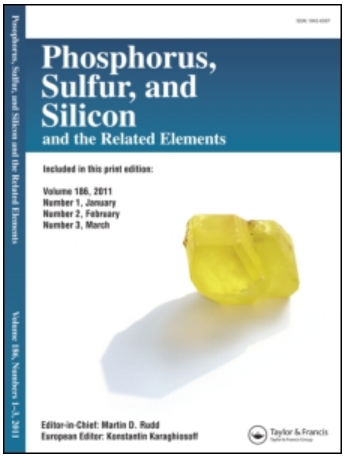

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A Novel Synthetic Route to New 1,2,4-Triazolo-1,3,5-triazin-4-ones Derivatives

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A Novel Synthetic Route to New 1,2,4-Triazolo-1,3,5-triazin-4-ones Derivatives

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The reaction of ethyl chloroformate with iminoesters derived from 3-aminotriazole, followed by amine or phenyl hydrazine condensation, leads to a variety of 1,2,4-triazolo-1,3,5-triazin-4-ones in a 60–85% overall yield.

Keywords 1,2,4-triazolo-1,3,5-triazin-4-ones; 3-amino-triazole; amine; Ethylchloroformate; iminoesters; phenyl hydrazine

INTRODUCTION

Its important to note here that triazolo-triazines and its derivatives are known for their useful properties, ranging from pharmacological and biological activities.[1–3] For instance, in recent years, some triazolo–triazine compounds have shown potent antitumor and antiviral activity.[4–8] Our interest for theses compounds is due to the well-known, interesting pharmaceuticals properties.

A variety of methods were used to obtain triazolo–triazine derivatives.[8–12]

RESULT AND DISCUSSION

We have successfully obtained substituted triazolo-triazine **3** or **4** starting from iminoesters **1** in a two-step transformation. Iminoesters **1** were treated with an equivalent of ethyl chloroformate in the presence of a small excess of pyridine in order to form N-3- (4-carbethoxy) triazolyl imidate **2**. Furthermore, the mixture of an excess of amine and compound **2** was heated under reflux for 4 h to transform them into triazolo-triazine **3**, presumably via the intermediate **A** (Scheme 1).

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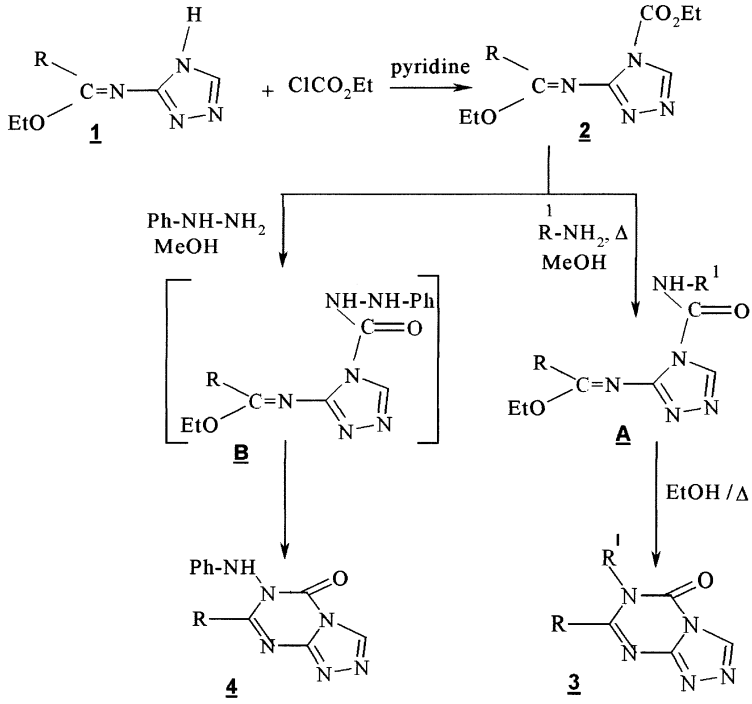

2	R	**3**	R	R^1	**4**	R
2a	Me	**3a**	Me	Ph	**4a**	Me
2b	Et	**3b**	Et	Ph	**4b**	Et
2c	Ph	**3c**	Me	Ph-CH_2		
A:	R- Ph, R^1= Pyridyl	**3d**	Et	Ph-CH_2		
		3e	Ph	Ph-CH_2		
		3f	Me	Pyridyl		
		3g	Ph	Pyridyl		

Ph-CH_2- :  Pyridyl : 

SCHEME 1

The condensation of phenyl hydrazine with compound **2** at r.t. leads to triazolo-triazine **4** after 5 days.

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

The structural features of our target compounds **3** or **4** were elucidated by IR and ^{1}H and ^{13}C spectral data.

The formation of compound **3** was confirmed by the IR spectra showing a strong band in the region of 1720–1740 cm^{-1} assigned to the

carbonyl group and another band in the region 1620 cm^{-1} assigned for C=N. The IR and ^1H NMR data confirm the structure of compound **4**.

The IR spectrum of **4** exhibited absorption bands for NH, C=N, and C=O groups. ^1H NMR spectrum recorded in DMSO—d_6 revealed a singlet in the region of $\delta = 7.5$–7.8, attributed to the NH proton.

The ^{13}C NMR spectra display the characteristic signals of all carbons.

From a mechanistic viewpoint, we have isolated one intermediate **A**. The attack of the carbon of the carbamate group by the nitrogen atom of the amine forms **A**. The latter undergoes intramolecular nucleophilic cyclization to give the derivatives of triazolotriazines **3** (Scheme 1).

The condensation of phenyl hydrazine and compound **2** at r.t. gives **4**; we could not isolate intermediate **B**.

EXPERIMENTAL

IR spectra were run in a $CHCl_3$ solution on a Perkin Elmer Paragon 1000 PC spectrometer.

^1H and ^{13}C NMR spectra were recorded with $CDCl_3$ or $(CD_3)_2SO$ as a solvent containing TMS on a Bruker 300 spectrometer. The chemical shifts are reported in ppm relative to TMS (internal reference). For the H 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** was obtained from the condensation of 3-amino-1,2,4-triazole with an excess of orthoester in the presence of acetic acid. The mixture was refluxed for 3 h; the solvent was evaporated under reduced pressure. The solid product so formed was filtered according to the published procedure.[13–15]

Synthesis of Imidates Type 2

To a mixture of 0.011 mol of imidate **1** and 0.012 mole of pyridine in 50 mL of anhydrous ether, 0.011 mol of ethyl chloroformate was added drop wise at 0°C. The mixture was stirred for 3 h. The pyridinium chlorhydrate obtained was filtered, and the solvent was removed under reduced pressure. The resulting solid was washed three times with anhydrous Et_2O and then used for further steps.

2a: Yield: 90%, m.p. = 110, IR ($CHCl_3$) $\nu_{CO} = 1770\ cm^{-1}$, $\nu_{CN} = 1660\ cm^{-1}$, NMR ^1H ($CDCl_3$): 8.7(s, 1H), 4.5(q, 4H), 1.4(t, 6H), 2.2(s, 3H).
2b: Yield: 80%, m.p. = 127°C, IR ($CHCl_3$) $\nu_{CO} = 1770\ cm^{-1}$, $\nu_{CN} = 1660\ cm^{-1}$, NMR ^1H ($CDCl_3$): 8.7(s, 1H), 4.5(q, 4H), 1.4(t, 9H), 2.5(q, 2H).
2c: Yield: 85%, m.p. = 63°C, IR ($CHCl_3$) $\nu_{CO} = 1770\ cm^{-1}$, $\nu_{CN} = 1660\ cm^{-1}$, NMR ^1H ($CDCl_3$): 8.5(s, 1H), 4.5(q, 4H), 1.4(t, 6H), 7.3(s, 5H).

Synthesis of Triazolo-Triazinones 3 and 4

Synthesis of 1,2,4-Triazolo-1,3,5-triazine-4-ones 3

The treatment of compound **2** with an excess of amine using methanol as a solvent and heating the mixture under reflux for 4 h gave **3**. The solvent was removed under reduced pressure; the solid product so formed was collected by filtration, dried, and recrystallized from ethanol to give **3**.

Intermediate **A**: Yield = 50% m.p. = 160°C, IR ($CHCl_3$ $\nu(cm^{-1})$): $\nu_{NH} = 3460$; $\nu_{C=N} = 1650$, $\nu_{C=O} = 1750$, ^1H NMR ($CDCl_3$): 4. 7(1, 2H); 7.3–7.6(mu, 9H); 9.8(s, 1H); 8.5(1, 1H); 1.4(t, 3H); 4.3(q, 2H).

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(q, 2H); 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.

Analyze	Calcd.:	%C = 55.6	% H = 4.5	% N = 29.0
	Found:	%C = 55.0	% 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(q, 2H); 4.6(1, 2H); 7.2–7.4(mu, 5H); 10(s, 1H). ^{13}C NMR ($CDCl_3$): 12.5; 29; 46; 128; 129; 130.7; 136.4; 141.2; 151; 157.5; 161.

3e: Yield = 60%, m.p. = 212°C, IR ($CHCl_3$, $\nu(cm^{-1})$): $\nu_{C=N} = 1610$, $\nu_{C=O} = 1720$, ^1H NMR ($CDCl_3$: 4.6(1, 2H); 7.2–8.6(mu, 10H); 9.6(s, 1H). ^{13}C NMR ($CDCl_3$): 47; 125; 128; 129; 130.7; 136.4; 141.2; 151; 156; 157.5; 164.

3f: Yield = 78% m.p. = 175°C, IR ($CHCl_3$, $\nu(cm^{-1})$): $\nu_{C=N} = 1620$, $\nu_{C=O} = 1725$, ^1H NMR ($CDCl_3$): 2.4(s, 3H); 4.7(1,2H); 7.2–7.6.(mu, 4H); 10(s, 1H).

3g: Yield = 75%, m.p. = 185°C, IR ($CHCl_3$ $\nu(cm^{-1})$): $\nu_{C=N} = 1620$, $\nu_{C=O} = 1725$, ^1H NMR ($CDCl_3$); 4.7(1, 2H); 7.2–7.6. (mu, 10H); 9.7(s, 1H).

Synthesis of Triazolo-Triazine 4

Treatment of iminoesters **2** with an excess of phenyl hydrazine at r.t. for 5 days in methanol gave **4**. The solvent was removed under reduced pressure, and the solid was crystallized in methanol.

4a Yield = 70%, m.p. = 225°C, IR (KBr, $\nu(cm^{-1})$): $\nu_{NH} = 3360$, $\nu_{C=N} = 1630$, $\nu_{C=O} = 1725$, ^1H NMR ($(CD_3)_2SO$): 2.1(s, 3H), 7–7.2(mu, 5H); 7.7(s 1H); 7.8(mu, 1H); 9.7(s, 1h).

4b Yield = 75%, m.p. = 205°C, IR (KBr $\nu(cm^{-1})$): $\nu_{NH} = 3360$ $\nu_{C=N}$ 1630, $\nu_{C=O}$ 1725, ^1H NMR ($(CD_3)_2SO$): 2.55(q, 2H), 1.2(t, 3H) 7–7.2 (mu, 5H); 7.7(s, 1H); 7.8(mu, 1H); 9.7(s, 1H).

REFERENCES

[1] F. Akahoshi, S. Takeda, T. Okada, M, Kajri, H. Nishimura, M. Suguira, Y. Inoue, C. Fukaya, Y. Naito, T. Imagawa, and N. Nakamura, *J. Med. Chem.*, **41,** 2985 (1998).

[2] R. Volpini, S. Costanzi, S. Vittori, G. Cristalli, and N. Klotzk, *Current Topics in Medicinal Chemistry*, **3,** 427 (2003).

[3] F. Leroux, B. J. Van Keulen, J. Daliers, N. Porrmury, and J. P. Henichart, *Biorg. Med. Chem.*, **7,** 509 (1999).

[4] M. Zwart, R. C. Vollinga, M. W. Beukers, D. F. Sleegers, J. K. Von Frijtag Drabbe Kûnzel, M. Groote, and Ad. P. Ijzerman, *Drug Development Research*, **48,** 95 (1999).

[5] K. A. Jacobson and X. D. Ji, *Drug Des Discovery*, **16,** 217 (1999).

[6] H. K. Peng, G. Yao, G. Sha, L. Wang, J. Vanvlijmen, and H. Bohne, *Journal of Medicinal Chemistry*, **47,** 6218 (2004).

[7] K. A. Jacobson and X. D. Ji, *Drug Des. Discovery* **16,** 89 (1999).

[8] A. R. Katritzky and C. W. Rees, Comprehensive Heterocyclic Chemistry, Vol. 5, (Pergamon Press, London, 1984).

[9] A. Dandia, K. Arya, and M. Sati, *Synth. Commun.*, **34,** 1141 (2004).

[10] Y. Miyamoto, H. Kohno, W. Pfleiderer, P. Boeger, and J. Wakabayashi, *Pesticide Sci.*, **20,** 119 (1995).

[11] H. Zohdi, *J. Chem. Res.*, **392,** 2378 (1997).

[12] A. Dandia, K. Arya, and M. Sati, *Synth. Commun.*, **34,** 1141 (2004).

[13] L. Claisen, *Ann. Chem*. **287,** 360 (1895).

[14] A. A. Matson, *J. Org. Chem.*, **42,** 1610 (1977).

[15] C. Ainsworth, *J. Amer. Chem. Soc.*, **87,** 5800 (1965).