Vol. 5 No. 4
Autumn 1994

SYNTHESIS OF SOME IMIDAZO [1, 2-b] [1, 2, 4] TRIAZINE AND N-ALKYLATED IMIDAZO [1, 2-b] [1, 2, 4]-TRIAZINES

M. M. Heravi[1], Y. Shirazi Beheshtiha[2] and M. Bakavoli[1]

[1] *Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, Islamic Republic of Iran*
[2] *Department of Chemistry, Alzahra University, Tehran, Islamic Republic of Iran*

Abstract

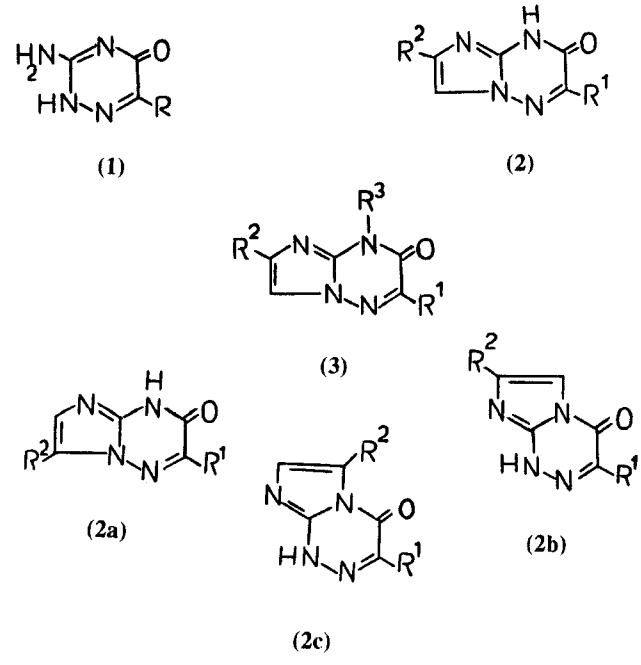
A number of 3-amino-1, 2, 4-triazin-5 (2H)- ones(1) were synthesized and condensed with α-haloketones to give 2,6-disubstituted imidazo [1, 2-b] [1, 2, 4]-triazin-3 (4H)-ones (2). These compounds were reacted further with α-haloketones to yield N-alkylated products (3).

Introduction

The chemistry of imidazo[1, 2-b] [1, 2, 4]-triazine has been intensively studied [1-9]. Imidazotriazines are biologically active agents [8-9]. Due to an interest in the synthesis and structural elucidation of bicyclic compounds derived from 1, 2, 4-triazine [10, 12] we now report the results of the synthesis of some new derivatives of (2) and their novel N-alkylated products.

Results and Discussion

3-Amino-1, 2, 4-triazin-5-(2H)-one(1; R = H) was made through the reaction of aminoguanidine and chloral hydrate with subsequent cyclization of the intermediate [13]. The 6-unsubstituted 1, 2, 4-triazine (1; R = H) was brominated by using a large excess of bromine to yield 3-amino-6-bromo-1, 2, 4-triazin-5(2H)-one (1; R = Br) [14]. The bromine atom could not be replaced by hydrazine hydrate but it was replaced by the morpholine group when the compound was refluxed in neat morpholine to afford (1; R = morpholino). The bromo compound (1: R = Br) was treated with sodium hydrogen sulphide to yield (1; R = SH). The latter was reacted with benzyl chloride in sodium carbonate solution to afford (1; R = $-SCH_2Ph$). This compound was reacted with phenacyl bromide in boiling DMF to afford a crystalline compound. For this compound four structures are possible. They are depicted in Scheme 1(2; 2a; 2b and 2c).

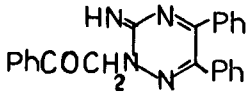


Scheme 1

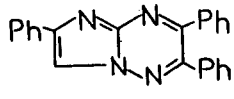
Keywords: Imidazotriazine-N-substituted

It has already been shown [4] that in the formation of imidazo-triazines nitrogen 2 is more reactive and is involved in the cyclization. That ruled out the possibility of the formation of [c] fusion structures (2b and 2c).

Although we could not isolate the intermediate in the formation of the imidazo triazine, it has been claimed that 5,6-diphenyl-3-imino-2-phenacyl-1, 2, 4, triazine (4) was isolated in mild conditions and cyclized to yield the corresponding imidazo [1, 2-b] [1, 2, 4]-triazine (5) [15].



(4)

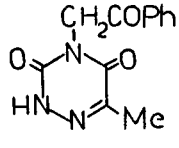


(5)

In addition, although it is now generally accepted that in most cases in heterocyclic compounds any imino-tantomers are present only in amounts too small to be deleted [16], the exceptions to this rule include triazinones [17, 18]. D. J. le Count and his co- workers have studied the IR spectra of a number of 1,2,4-triazinones and their results show that the imino-tantomers of such systems are capable of existence [19]. This result suggests that the initial reaction may have occurred at the halogen atom thus ruling out the formation of (2a).

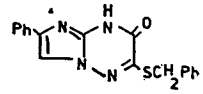
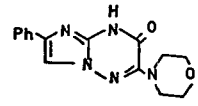
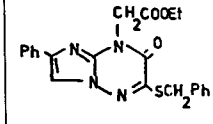
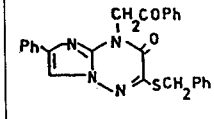
Based on the available spectral data and considering [4] and [15], we assigned the imidazo [1, 2-b][1,2,4] triazine (2; R^1=morpholino, -SCH_2Ph; R^2=Ph, $C_6H_4Brp_m$ structure for the product.

Reaction of (2; R^1=SCH_2Ph, R^2=Ph) with phenacyl bromide in the presence of triethylamine was investigated and it gave a crystalline product. The ^1H NMR spectrum of this compound showed a chemical shift for the methylene group which was similar to that of the 6-methyl-4-phenacyl-1,2,4-triazine -3,5(2H, 4H)-dione (6) [16]. Based on this comparison, we can conclude that the substitution has taken place on nitrogen 4 of the 1,2,4-triazine ring and structure (3) can be suggested for the obtained compound. Typical ^1H NMR spectral data of (2) and (3) is shown in Table 1.



(6)

Table 1. ^1H NMR spectra of some imidazo[1,2-b] 1,2,4-triazines

Compound	Signal	Assignment
	4.28, s, 2H 7.2-7.4, m. 10H 7.95, s, 1H	CH_2 2Ph CH
	3.3-3.7, 2t, 8H 7.1-7.3, m, 5H 7.79, s, 1H	C_4H_8 Ph CH
	1.21, t, 3H 4.3, s, 2H 4.25, qr, 2H 5.3, s, 2H 7.3-7.5, m, 10H 8.25, s, 1H	CH_2-Me CH_2 CH_2-Me CH_2 2Ph CH
	4.29, s, 2H 6.12, s, 2H 7.4-7.6, m, 15H 8.31, s, 1H	CH_2 CH_2 3Ph CH

Experimental Section

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. ^1H NMR spectra were measured on a Perkin-Elmer R32/90 MHZ model at normal temperature unless specified otherwise using tetramethylsilane as an internal standard. d_6DMSO was used as solvent for all compounds. Infrared spectra were recorded using the Nujol mull technique on a Perkin-Elmer 297 double beam spectrometer. Mass spectra were recorded on an AEIMS 902 S mass spectrometer. Mieroanalyses were performed by Butterworth Laboratories Ltd., Teddington, Middlesex, England.

3-Amino-6-bromo-1,2,4-triazin-5(2H)-one(1, R=Br)

Bromine (13 g; 0.081 mole) was added dropwise with stirring to a suspension of 3-amino-1,2,4-triazine (8 g, 0.063 mole) in water (400 ml). The reaction mixture was stirred at room temperature for 2 h. The precipitated solid was collected, washed thoroughly with water and dried in an oven to give the title

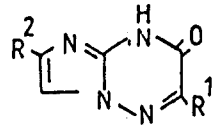
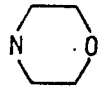
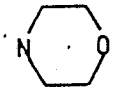


Table 2. 2,6-Disubstituted imidazo[1,2-b]1,2,4-triazin-3(4H)-ones

R^1	R^2	m.p.(°)	Crystn. Solvent	Yield	Halide used	Found % C	Found % H	Found % N	Requires % C	Requires % H	Requires % N
SCH_2Ph	Ph	over 300	DMF	64%	$PhCOCH_2Br$	64.30	4.22	16.75	64.65	4.21	16.75
SCH_2Ph	C_6H_4Br	285	DMF	60%	$pC_6H_4BrCOCH_2Br$	52.18	3.26	13.62	52.21	3.16	13.59
	Ph	290 decomp	Aqueous DMF	60%	$PhCOCH_2Br$	60.75	5.07	23.67	60.60	5.08	23.55
	C_6H_4Br	281-282	Aqueous DMF	57%	$pC_6H_4BrCOCH_2Br$	M	375		M	375	

compound (8.9 g; 65%) m. p. 253-254°C lit [14] 258-259°C (from aqueous dimethylsulphoxide).

3-Amino-6-morpholino-1,2,4-triazin-5(2H)-one(1;R = morpholino)

3-Amino-6-bromo-1,2,4-triazin-5(2H)-one(2 g, 0.0097 mole) was refluxed in morpholine (20 ml) for 15 min. The reaction mixture was cooled to room temperature to give a white solid which was filtered off, washed with water and dried in an oven to yield the title compound (1.75; 89%) m. p. decomp. over 300°C [Found; C;42.64; H, 5.56;N 35.51 M^+ (mass spectrum) 197, $C_7H_{11}N_5O_2$ requires; C, 42.64; H 5.62; N, 35,51; M, 197 ^1H NMR [d_6-DMSO] (3,3 and 3,65 d, d, 8 H, C_4H_8), 6.42 (S, 2H, NH_2).

3-Amino-6-mercapto-1,2,4-triazin-5(2H)-one (1, R^1=SH)

3-Amino-6-bromo-1,2,4-triazin-5(2H)-one (5 g; 0.024 mole) and sodium hydrogen sulphide (10 g; 0.178 mole) were dissolved in hot water (100 ml). The reaction mixture was stirred at room temperature for 2 h and acidified with dilute hydrochloric acid to pH 3 to give a pale yellow solid. The solid was redissolved by addition of potassium carbonate and filtered through silica. The filtrate was acidified by the addition of hydrochloric acid (30 ml, 1N). The yellow solid was filtered off and washed with water to give the title compound (32. g; 85%). m. p. 258-259°C (decomp) (from water).

3-Amino-6-benzylmercapto-1,2,4-triazin-5(2 H)-one (1; R^1=SCH_2 Ph)

3-Amino-6-mercapto-1,2,4-triazin-5(4H)-one (3 g, 0.018 mole) was dissolved in potassium carbonate solution [potassium carbonate (2 g 0.014 mole) in water (20 ml)] and benzyl chloride (2.52 g; 0.02 mole) was added dropwise. The reaction mixture was stirred for 2 h and subsequently chilled in an ice bath for a further 1 h. The precipitated white solid was filtered off, washed thoroughly with water and dried in an oven to afford the title compound (3.2 g; 65%) m.p. 313-315°C (from dimethylsulphoxide). [Found; C, 51.30; H,4.38; N, 24.04; M^+(mass spectrum) 234, $C_{10}H_{10}N_4$50, requires; C; 51.27; H,4.30; N, 23.91] ^1H NMR [d_6-DMSO] 4:09(S, 2H, CH_2) 6.78 (S, 2H, NH_2) 7.34 (m, 5H, Ph).

2,6-Disubstituted imidazo-[1,2,4]-triazin 3(4 H)-ones(2)

The appropriate 3-amino-1,2,4-triazin-5(2 H)-one(1) (0.01 mole) was dissolved in hot dimethylformamide (20 ml) and appropriate α-halogenoketone (0.01 mole) and triethylamine (10 ml)

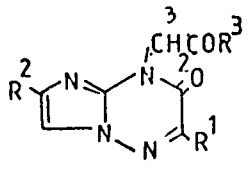
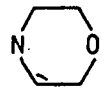
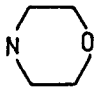


Table 3. 2,4,6-Trisubstituted imidazo[1,2-b]1,2,4-triazin-3(4H)-ones

R^1	R^2	R^3	m.p.(°)	Yield	Halide used	Found % C	H	N	Requires % C	H	N
SCH_2Ph	Ph	$CH_2COC_6H_4Brp$	210	48%	$pBrC_6H_4COCH_2Br$	58.73	3.71	10.70	58.76	3.60	10.54
SCH_2Ph	Ph	CH_2COOEt	220-222	35%	$ClCH_2COOEt$	M	420.1255		M	420.1255	
	Ph	CH_2COPh	235-236	52%	$PhCOCH_2Br$	66.48	5.08	16.67	66.50	5.10	16.86
	Ph	$CH_2COC_6H_4Brp$	222-224	47%	$pBrC_6H_4COCH_2Br$	M	493		M	493	

were added. The reaction mixture was refluxed for 2 h and cooled to room temperature. The solution was poured into water (20 ml) and the solid obtained was filtered off, washed with water and crystallized from aqueous dimethylformamide. Melting points, yields, halides used and elemental analysis of the products are reported in Table 2.

2,4,6-Trisubstituted imidazo-[1,2,-b]-[1,2,4]-triazin-3-ones(3)

The appropriate 2,6-disubstituted imidazo-[1,2,4]-triazin-3 (4 H) -one (0.01 mole) along with α-halogeno compound (0.01 mole) and triethylamine (10 ml) were dissolved in dimethylformamide (20 ml). The reaction mixture was refluxed for 2 h and cooled to room temperature. The solution was poured into water (20 ml) and the precipitated solid was filtered off, washed with water, crystallized from aqueous dimethylformamide to obtain the desired compound. Melting points, yields, halides used and elemental analysis of the products are reported in Table 3.

Acknowledgements

We would like to thank Mrs. R. Maynard and Mrs. J. Martin for making the mass spectra measurement and Mr. R. Hayes and Mr. A. Moores, who recorded the ^1H NMR.

References

1. Gevaertd Photo Production, Brit Pat, (Aug 11, 1965) 1001064, CA., **65**, 20152b, (1966).
2. Werhel, L. M. and Zamora, M. L. *J. Heterocyclic Chem.*, **2**, 287, (1965).
3. Werhel, L. M. and Zamora, M. L. *Ibid.*, **2**, 303, (1965).
4. Lalezari, I. and Levi, Y, *Ibid.*, **11**, 327, (1974).
5. Keen, B. T. and Krass, D. K. *Ibid.*, **13**, 807, (1976).
6. Loev, B. and Goodman, G. *Tetrahedron Lett*, 789, (1988).
7. Saraswathi, T. V. and Srinvasan, V. R. *Ibid.*, 2315, (1971).
8. Kruglenko, V. P., Timoshin, A. A., Klyuev, N. A., Logacher, E. V. and Povslynoi, M. V. *Kihn, Geterotsikl Soedin*, **7**, 981, 1986 (Rues) C. A., 106, 176341 h, (1987).
9. Dovzhenko, S. A., Pozmogova, G. E., Esipor, S. E., Aleksandrov, G..G., Klyvev, N. A. and Chernysher, A. I. *Amtobipt Med. Bioteknol.*, **31**, (4), 251, (1986) (Russ), C. A. 106, 50161f, (1987).
10. Heravi, M. M. and Bakavoli, M. *J. Research in Sci. and Tech.*, **17**, 28, (1990) (Farsi).
11. Heravi, M. M. and Bakavoli, M. *J. Sci. I. R. Iran*, **5**, 361, (1990).
12. Heravi, M. M. and Bakavoli, M. *Ibid.*, (In press)
13. Gut D. Hesoun, J. and Novacek, A. Collection *Czech. Chem. Commun.*, **31**: (5), 2014, C. A. 65, 714 h, (1966).
14. Oeilly Allen, M. and Hanbury's Research Ltd., Ware, Herts., U. K.
15. Povstyanoi, M. V., Kruglenko, V. P. and Kochergin, P.

M. *Ukr. Khem. Zh.*, **42**, 1166, (1976).
16. Katritzky, A. R. and Ambler, A. P. In *Physical methods in heterocyclic chemistry*, (ed. A. R. Katritzky), p. 323, Vol. II, Academic Press, New York, (1963).
17. Pitha, J., Fiedler, P. and Gut, J. *Coll. Czech. Chem. Comm.*, **31**, 1864, (1966).
18. Katritzky, A. R. *Chimia*, **24**, 134, (1970).
19. Le Count, D. J. and Taylor, P. J. *Tetrahedron*, **31**, 433, (1975).
20. Heravi, M. M. and Bakavoli, M. Ring cleavage of triazinotriazines submitted to *Iran J. Chem. Eng.*, (1992).