CHEMISTRY OF 1,2,4-TRIAZINE. II.*
SYNTHESIS OF SUBSTITUTED 5-AMINO-1,2,4-TRIAZINES

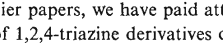
V. UCHYTILOVÁ, P. FIEDLER and J. GUT

Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague 6

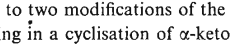
Received June 22nd, 1971

Condensation of acetyl cyanide or benzoyl cyanide with acetamidrazone or benzamidrazone in the presence of hydrogen chloride leads to 1-cyano-4-amino-2,3-diaza-1,3-butadienes *Ia—d* substituted at positions 1 and 4 by methyl and/or phenyl groups. On treatment with methanolic sodium methoxide or by the action of elevated temperatures, compounds *Ia—d* are converted to the corresponding 3,6-disubstituted 5-amino-1,2,4-triazines *IIa—d*.

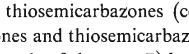
In our earlier papers, we have paid attention to two modifications of the most usual synthesis of 1,2,4-triazine derivatives consisting in a cyclisation of α-keto acid semicarbazones or thiosemicarbazones (compounds of the type *A*). Thus, cyclisation of semicarbazones and thiosemicarbazones of α-keto acid nitriles[1] and glyoxylic acid nitrile[2] (compounds of the type *B*) leads to 5-amino-2,3-dihydro-1,2,4-triazin-3-ones while the cyclisation of α-keto acid amidrazones[3] (compounds of the type *C*) affords 2,5-dihydro-1,2,4-triazin-5-ones. In the present paper, we wish to report the cyclisation of "α-keto acid nitrile amidrazones", *i.e.*, substituted 1-cyano-4-amino-2,3-diaza-1,3-butadienes *I* leading to 3,6-disubstituted 5-amino-1,2,4-triazines *II*; this cyclisation represents a combination of both the above mentioned modifications.



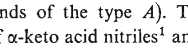
A, X = O, S



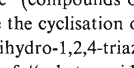
B, X = O, S



C



I



II

In formulae *I* and *II*:

a, $R^1 = R^2 = C_6H_5$ — *c*, $R^1 = C_6H_5$; $R^2 = CH_3$

b, $R^1 = CH_3$; $R^2 = C_6H_5$ — *d*, $R^1 = R^2 = CH_3$

* Part I: This Journal *36*, 1955 (1971).

Some of substituted 1-cyano-4-amino-2,3-diaza-1,3-butadienes *I* which serve in the present procedure as intermediates, have been prepared some time ago by a two-step synthesis from 3,5-disubstituted 4-nitrosopyrazoles[4]. This synthesis is unequivocal only with equal substituents R^1 and R^2, while with different substituents R^1 and R^2 the synthesis may lead to two isomers.

Condensation of amidrazones with acyl cyanides (α-keto acid nitriles) is simpler and gives unambigous products even with starting compounds possessing unequal substituents. Since, however, both the reaction components tend to reactions of another type, it is important to find out suitable reaction conditions. Acyl cyanides react with the amino group as acylating agents[5]; thus, on mixing *e.g.* benzoyl cyanide with benzamidrazone in dioxane, 1-benzoylbenzamidrazone is exclusively obtained. As observed earlier[1,6-8], this formation may be suppressed by the presence of hydrogen chloride. Under these conditions and at room temperature (the low temperature suppresses autocondensation and hydrolytical reactions of amidrazones[9]), the hydrochlorides of compounds *I* are obtained in reasonable yields. In aqueous solutions, these hydrochlorides are hydrolysed to a considerable extent. Thus especially 1,4-diphenyl-1-cyano-4-amino-2,3-diaza-1,3-butadiene (*Ia*) is deposited directly from the aqueous solution of this hydrochloride and may be extracted with a poorly polar solvent. In the case of other derivatives, namely, 5-phenyl-2-cyano-5-amino-3,4-diaza-2,4-pentadiene (*Ib*), 1-phenyl-1-cyano-4-amino-2,3-diaza-1,3-pentadiene (*Ic*), and 2-cyano-5-amino-3,4-diaza-2,4-hexadiene (*Id*) it is more advantageous to isolate the free bases by extraction of solutions previously neutralised with sodium carbonate or silver carbonate. In accordance with earlier findings[4], compounds *Ia–c* the azine system of which is conjugated with one or two benzene nuclei, are yellow. This observation along with infrared spectral data may be regarded as confirmation of the structure *I*.

The infrared spectra of compounds *Ia–d* in chloroform solutions are as follows:

Compound	$\nu(NH_2)$	$\nu(C\equiv N)$	$\nu(C{=}N) + \delta(NH_2)$
Ia	3 523, 3 400	2 221	1 609, 1 496
Ib	3 521, 3 391	2 226	1 611, 1 513
Ic	3 527, 3 405	2 221	1 615, 1 514
Id	3 527, 3 398	2 227	1 618, 1 536

Bands of the antisymmetrical and symmetrical vibration $\nu(NH_2)$ and the $\nu(C\equiv N)$ band confirm the presence of these groups. The symmetrically substituted system of $>C{=}N{-}N{=}C<$ bonds in azines of aldehydes and ketones[11] exhibits in the infrared spectrum a single $\nu(C{=}N)$ band in the $1665-1610\ cm^{-1}$ region. In addition to bands due to phenyl substituents the asymmetrically substituted compounds *Ia–d* show in the $1500-1700\ cm^{-1}$ region two intensive bands attributable to the in-phase and out-of-phase $\nu(C{=}N)$ vibrations with some part of $\delta(NH_2)$.

Fusco and Rossi[4] report also the cyclisation of compound *Ia* to the corresponding 5-amino-1,2,4-triazine *IIa* on refluxing in aqueous–ethanolic sodium hydroxide. Despite the fact that the cyclisation is claimed to proceed in relatively satisfactory yields, there is still danger of a hydrolysis of the nitrile group as the primary side-reaction and hydrolysis of the amino group on the resulting product as the secondary side-reaction. It will be shown below that the latter hydrolysis may be performed on a preparative scale. Consequently, methanolic sodium methoxide was used for the preparative cyclisation of compounds *I* to aminotriazines *II*. As shown by thin-layer chromatography, the yields obtained by the sodium methoxide method are almost quantitative. In accordance with earlier considerations[1,10] and analogously to the cyclisation of acyl nitrile guanylhydrazones, compounds *I* may be cyclised also thermally, *e.g.*, on refluxing in a suitable higher-boiling solvent or on heating in the solid state. For this reason, the melting points of compounds *I* are not sharp. Depending on conditions of the melting point determination (rate of heating and the like), an additional heating may lead to resolidification of the specimen; the final melting point value is then equal to the melting point value of the cyclisation product *II*.* The chemical evidence of the structure *II* for the aminotriazines consisted in hydrolysis of compounds *IIa* and *IIb* by dilute aqueous sodium hydroxide under the formation of the known 3,6-diphenyl-2,5-dihydro-1,1,4-triazin-5-one[4] and 3-phenyl-6-methyl-2,5-dihydro-1,2,4-triazin-5-one[3], resp. In the procedure[4], the hydrolysis was performed with 48% hydrobromic acid which was claimed as the only suitable hydrolytical agent.

The proposed structure of aminotriazines *IIa–d* also corresponds to their infrared spectra:

Compound	$\nu(NH_2)$	$\delta(NH_2)$	ν(ring)
IIa	3 521, 3 406	1 606	1 539, 1 514, 1 443, 1 401
IIb	3 534, 3 416	1 613	1 549, 1 536, 1 443, 1 401
IIc	3 520, 3 405	1 606	1 543, 1 518, 1 443, 1 411
IId	3 531, 3 415	1 616	1 556, 1 540, 1 442, 1 415

They exhibit bands due to stretching and deformation vibration of the amino group while the ν(N—H) bands due to the exocyclic imino group were absent. The aromatic

* The discrepancy between our melting point value of compound *Ib* (93–95°C) and that reported in the literature[4] (222°C) might be explained by this behaviour but the melting point value of the authentic cyclic product *IIb* was by us determined as 202–203°C. Since the possibility of an isomeric substance *IIc* (m.p. 229–231°C) seems to be reliably excluded by Fusco[4], the 222°C value must be an error.

character of compounds *IIa–d* is also confirmed by the presence of bands due to ring stretching vibrations of the triazine ring at wavenumbers very similar to those of 1,2,4-triazine alone[13]. A discussion of spectral data contains the paper[12].

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). Analytical samples were dried at room temperature and 0·1 Torr for 8 h. Infrared spectra were taken in chloroform on a Perkin-Elmer 621 apparatus. In view of the low solubility of most test substances, the concentration of about 0·5% was used (0·5 mm cells).

Benzamidrazone

A suspension of benziminoethyl ether hydrochloride (9·28 g; 50 mmol) in 5M-NaOH (15 ml) and ether (30 ml) was shaken until the solid dissolved, the aqueous layer separated, and extracted with three 40 ml portions of ether. The ethereal layers were combined, dried over magnesium sulfate, and treated with hydrazine (1·6 g; 50 mmol) in methanol. The mixture was kept at 3°C for 12 hours and evaporated to dryness under diminished pressure. The residue was extracted with three 50 ml portions of ether, the extract filtered, concentrated to the volume of about 50 ml, the concentrate diluted with light petroleum, and the mixture kept at 0°C to deposit 3·8 g (56·2%) of benzamidrazone, m.p. 73–75°C (ref.[14], 78–79°C).

1,4-Diphenyl-1-cyano-4-amino-2,3-diaza-1,3-butadiene (*Ia*)

A mixture of benzamidrazone (0·67 g; 5 mmol), dimethylformamide (15 ml), ethereal hydrogen chloride (0·36 g of HCl; 10 mmol), and benzoyl cyanide (0·65 g; 5 mmol) was allowed to stand at room temperature for 7 days and then evaporated to dryness under diminished pressure. The residue was washed with four 30 ml portions of ether, dried *in vacuo*, triturated with water (30 ml), and the precipitated product extracted with six 50 ml portions of benzene. The combined extracts were evaporated and the residue crystallised from benzene. For the yield, m.p. value and analysis see Table I.

5-Phenyl-2-cyano-5-amino-3,4-diaza-2,4-pentadiene (*Ib*)

A solution of benzamidrazone (1·35 g; 10 mmol) in dioxane (20 ml) was treated with ethereal hydrogen chloride (0·72 g of HCl; 20 mmol) and acetyl cyanide (0·69 g; 10 mmol). The resulting suspension was stirred at room temperature for 46 hours and then evaporated to dryness under diminished pressure. The residual hydrochloride (2·3 g) was dissolved in water (35 ml), the solution made alkaline with 3% aqueous sodium carbonate, and extracted with four 50 ml portions of benzene. The extracts were combined, concentrated, the concentrate applied to a column of silica gel (15 g), and the first yellow band eluted with 600 ml of benzene. The eluate was evaporated and the residue crystallised from cold benzene by a gradual addition of light petroleum.

1-Phenyl-1-cyano-4-amino-2,3-diaza-1,3-pentadiene (*Ic*)

A mixture of acetamidrazone hydrochloride[15] (1·09 g; 10 mmol), dimethylformamide (25 ml), ethereal hydrogen chloride (0·36 g of HCl; 10 mmol), and benzoyl cyanide (1·31 g; 10 mmol) was stirred for about 3 hours, the resulting solution allowed to stand at room temperature for 7 days, and then evaporated to dryness under diminished pressure. The residue was washed with three 10 ml portions of ether, dried, and crystallised from a mixture of ethanol and ether to afford 2 g

TABLE I

Disubstituted 2,3-Diaza-1,3-butadienes *I* and 5-Amino-1,2,4-triazines *II*

Compound (Yield, %)	Formula (m.w.)	Calculated/Found % C	% H	% N	M.P., °C (solvent)
Ia (78·8)	$C_{15}H_{12}N_4$ (248·3)	72·56 72·35	4·87 4·58	22·57 22·80	165—170[a] (benzene)
Ib (61·2)	$C_{10}H_{10}N_4$ (186·2)	64·50 64·61	5·41 5·65	30·09 29·98	93— 95[b] (benzene–light petroleum)
Ic (77·2)	$C_{10}H_{10}N_4$ (186·2)	64·50 64·90	5·41 5·83	30·09 30·57	128—130 (ethyl acetate–light petroleum)
Id (55·8)	$C_5H_8N_4$ (124·1)	48·37 48·43	6·50 6·43	45·13 45·45	106—109 (benzene–light petroleum)
IIa (91·5)	$C_{15}H_{12}N_4$ (248·3)	72·56 72·54	4·87 4·66	22·57 22·78	221—223[c] (dioxane)
IIb (75·3)	$C_{10}H_{10}N_4$ (186·2)	64·50 64·24	5·41 5·30	30·09 30·18	202—203 (toluene)
IIc (70·4)	$C_{10}H_{10}N_4$ (186·2)	64·50 64·22	5·41 5·52	30·09 30·12	229—231 (dioxane)
IId (95·5)	$C_5H_8N_4$ (124·1)	48·37 48·40	6·50 6·48	45·13 45·47	225—226 (ethyl acetate)

[a]Reported[4], m.p. 170°C (uncorr.); [b]reported[4], m.p. 222°C; [c]reported[4], m.p. 219°C (uncorr.)

of the hydrochloride of compound *Ic*. The hydrochloride was dissolved in water (20 ml), the solution made alkaline with 3% aqueous sodium carbonate, and the precipitate extracted with three 50-ml portions of ether. The extracts were evaporated under diminished pressure and the residue crystallised from cold ethyl acetate by a gradual addition of light petroleum. The mother liquors were evaporated to a small volume and processed similarly.

2-Cyano-5-amino-3,4-diaza-2,4-hexadiene (*Id*)

A suspension of acetamidrazone hydrochloride[15] (0·55 g; 5 mmol), dioxane (10 ml), ethereal hydrogen chloride (0·18 g of HCl; 5 mmol), and acetyl cyanide (0·34 g; 5 mmol) was stirred at room temperature for 24 hours and evaporated to dryness under diminished pressure. The residue (0·86 g) was mixed with ethanol (60 ml) and silver carbonate (4·4g), and the resulting suspension stirred for 1 hour. The solid portion was filtered off and the filtrate was evaporated. The residue

was purified on a column of silica gel (7·5 g) in ethyl acetate–bencene (2 : 3). The effluent (about 600 ml) was evaporated under diminished pressure and the residue crystallised from a mixture of benzene and light petroleum.

Preparation of 5-Amino-1,2,4-Triazines *II*

Compound *Ia—d* (1 mmol) was refluxed with 1M methanolic sodium methoxide (1 ml) in methanol (5 ml) for 90 min. After this period of time the cyclisation was complete, as shown by chromatography on a thin layer of silica gel. With compounds *IIa—c*, the solution was evaporated to dryness under diminished pressure, the residue triturated with water (2 ml), the solid portion collected with suction, and washed with water till neutral. With compound *IId*, the solution was applied to a column of Amberlite IRC-50 (H^+) ion exchange resin (5 ml), the product eluted with methanol (about 160 ml), and the eluate evaporated.

Hydrolysis. A suspension of the aminotriazine *IIa* or *IIb* (1 mmol) in aqueous sodium hydroxide (1·5 g in 25 ml of water) was refluxed for 2·5 hours (*IIa*) or 1 hour (*IIb*). The resulting solution was filtered while hot, the filtrate acidified with hydrochloric acid, the precipitate collected with suction, and purified by crystallisation, 3,6-Diphenyl-2,5-dihydro-1,2,4-triazin-5-one, m.p. 282—283°C (dioxane); reported[4], m.p. 274—276°C. 3-Phenyl-6-methyl-2,5-dihydro-1,2,4-triazin-5-one, m.p. 243—246°C (water); reported[3], m.p. 245—247°C.

Elemental analyses were performed in the Analytical Department (Dr J. Horáček, Head) of this Institute.

REFERENCES

1. Beránek J., Gut J.: This Journal *34*, 2306 (1969).
2. Uchytilová V., Gut J.: This Journal *36*, 2383 (1971).
3. Uchytilová V., Fiedler P., Prystaš M., Gut J.: This Journal *36*, 1955 (1971).
4. Fusco R., Rossi S.: Tetrahedron *3*, 209 (1958).
5. Dornow A., Theidel H.: Chem. Ber. *88*, 1267 (1955).
6. Thesing J., Witzel D.: Chem. Ber. *88*, 117 (1955).
7. Beyer H., Pyl T., Wünsch K. H.: Chem. Ber. *93*, 2209 (1960).
8. Settepani J. A., Bořkovec A. B.: J. Heterocyclic Chem. *3*, 188 (1966).
9. Neilson D. G., Roger R., Heatlie J. W. M., Newlands L. R.: Chem. Rev. *70*, 151 (1970).
10. Gut J., Hesoun D., Nováček A.: This Journal *31*, 2014 (1966).
11. Frederickson L. D., jr: Anal. Chem. *36*, 1349 (1964).
12. Fiedler P., Uchytilová V., Gut J.: This Journal, in press.
13. Neunhoeffer H., Hennig H.: Chem. Ber. *101*, 3952 (1968).
14. Burg van der W. J.: Rec. Trav. Chim. *74*, 257 (1955).
15. Oberhummer W.: Monatsh. *63*, 285 (1933).

Translated by J. Pliml.