A CONVENIENT SYNTHESIS OF 2-ALKYL- and 2-ARYLAMINO-4-ARYL-5-CYANOTHIAZOLES

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Abstract - The reactions of a series of para-substituted 3-amino-3-aryl-propenenitriles 1a-f with N-phenyl- (2a) and N-methyl-S-chloroisothiocarbamoyl chloride (2b), followed by triethylamine treatment, provide 2-phenyl- and 2-methyl-4-aryl-5-cyanothiazoles 3a-i. N-Monosubstituted enaminonitriles 1g,h react with 2a affording 3-substituted 2-phenylimino-Δ^4-thiazolines 6a,b, but in very poor yields. A mechanism which accounts for the formation of thiazole and thiazoline structures is presented.

Pursuing our continous interest in exploring the potential, scope and limitations of 3-amino-3-arylpropenenitriles in heterocyclic synthesis, [1-5] in this paper we wish to report our recent investigations on the reactions of a series of para-substituted enaminonitriles 1a-f with N-phenyl- (2a) and N-methyl-S-chloroisothiocarbamoyl chloride (2b).[6] The work develops a novel synthetic approach to 2-aryl- and 2-alkylamino-4-aryl-5-cyanothiazoles 3, which appear to be of pharmaceutical interest.

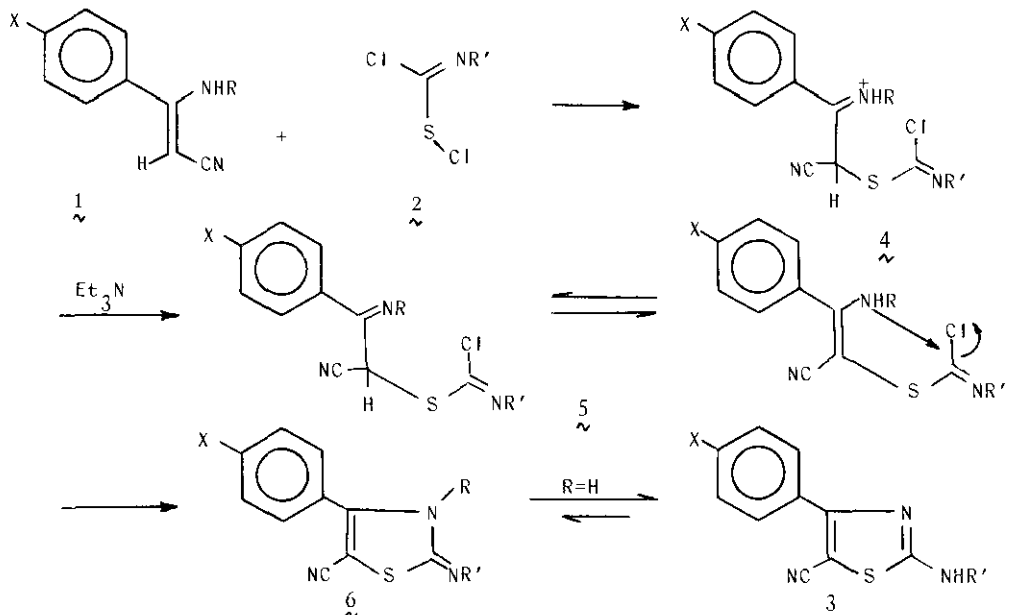
Typically thiazoles 3 were isolated by column chromatography of crudes derived from the reaction mixtures of 1 with 2 followed by treatment with triethylamine. Optimum yields (Table) were obtained by adding to an ice-cooled solution of 1 in chloroform an equimolar amount of freshly prepared 2 in the same solvent under stirring and an atmosphere of nitrogen. A 2:1 ratio of 2b to 1 was however required because of the low stability of 2b.[6]

The structures of thiazoles 3 relied upon elemental analysis, ir, ^{1}H nmr and mass spectra. In addition to the bands of aromatic C=C and C=N bonds of phenyl and thiazole rings in the region 1620-1515 cm^{-1}, ir spectra exhibited the N-H band around 3300 cm^{-1} and C≡N band around 2200 cm^{-1}. ^{1}H nmr spectra of derivatives 3a-f consisted of the trivial signals relative to methyl protons of phenyl substituents and phenyl protons. Those of derivatives 3g-i, besides the phenyl substituent and phenyl protons, showed a doublet around 3.0 δ for methylamino protons which converted

into a singlet upon treatment with D_2O. The amino proton was observed only in the case of derivative 3g as a broad signal in the aromatic region, while in all the other cases it was evidenced by differential integration of aromatic signals before and after the isotopic exchange. Mass spectra exhibited molecular ions as base peaks and two intense peaks corresponding to $(ArC{\equiv}NH)^+$ ions and to thiirenium ions deriving from the fission of the nucleus at 1,2- and 3,4-bonds. The mass spectra of 2-phenylamino derivatives 3a-f were characterized by the presence of a relatively abundant signal attributable to $(PhCNS)^+$ ion, while those of 2-methylamino derivatives 3g-i showed characteristic $(M-28)^+$ ions, which probably arise from the loss of the CH_2N radical from the methylamino side chain.[7,8]

Thiazoles structures 3a,g were confirmed by the Hantzsch's synthesis based on 1-bromo-1-cyanoacetophenone and N-phenyl- and N-methylthioureas. Their yields wer however lower than those isolated by the above procedure.

Based on the accumulated evidences on the reactivity of 1[3,4] and the chemistry of 2, which parallels that of sulfenyl chlorides,[6] the formation of thiazoles 3 is consistent with an initial substitution at the sulfenyl sulphur, yielding the cations 4. Deprotonation of 4 upon treatment with triethylamine causes an intramolecular cyclization of 5 to give the Δ^4-thiazolines 6. These latter exist predominantly in the tautomeric thiazole forms 3 in agreement with the found and available[9] experimental data (Scheme). All attemps to isolate cations 4 were unsucessful; in all cases cations 4 fragmented into complex mixtures of products.



R= H, C_6H_5, C_6H_{11}; R'= C_6H_5, CH_3; X= H, CF_3, Cl, CH_3, OCH_3, $N(CH_3)_2$

Scheme

The potential of this synthetic approach was further explored for the construction of 3-aryl- and 3-alkyl-substituted Δ^4-thiazolines 6. Thus N-phenyl- and N-cyclohexyl-substituted enamines 1g,h were allowed to react with 2a under the same experimental conditions used for 1a-f. The expected thiazolines 6a,b were isolated, but in very poor yields, together with unreacted starting enamines and mixtures of numerous products. This fact suggested that the low yields of 6a,b could be ascribed to steric effects retarding the ring closure of unisolable intermediates 5.

The structure of thiazolines 6a,b were supported by elemental analysis, ir, ^{1}H nmr and mass spectra. Ir spectra showed absorptions around 2200 cm^{-1} for the C≡N bond and in the range 1620-1560 cm^{-1} for the exocyclic C=N imino bond and C=C bonds of phenyl and thiazoline rings. ^{1}H nmr spectra of 6a showed only aromatic signals in the range 7.2-8.1 δ, while that of 6b showed the signals for cyclohexyl protons in the range 1.1-1.9 δ, in addition to those of phenyl protons at 7.3-7.5 δ. The mass spectra of thiazolines 6a,b gave molecular ions as base peaks and a series of fragment ions which was dominated by ions formed by fission of the nucleus at the 2,3- and 4,5-bonds.

Our synthetic approach to N-monosubstituted 2-amino-4-aryl-5-cyanothiazoles 3, appears as useful and convenient alternative route to the classical Hantzsch's synthesis. It affords more satisfactory yields and allows for sparing the conversion of isothiocyanates into N-monosubstituted thioureas which are required for the Hantzsch's procedure.

EXPERIMENTAL

Melting points were obtained on a Kofler hot stage apparatus, and are uncorrected. Ir spectra were run on a Perkin-Elmer 281 spectophotometer using KBr discs. ^{1}H Nmr spectra were recorded on a Bruker WP 80 FT spectrometer using a mixture of $CDCl_3$-DMSO-d_6 as solvent and Me_4Si as internal standard. Mass spectra were obtained with a LKB 9000 S spectrometer at 70 eV using a direct-inlet system. Elemental analyses were performed on a Carlo Erba Elemental Analyzer mod. 1106, and were within ±0.4% of the theoretical values. For thin-layer and column chromatography silica gel GF_{254} was used.

Enaminonitrile 1a and phenyl- and methyl isothiocyanate were commercially available (Aldrich). Enamines 1b-h were prepared according the previously described procedures.[1,2]

General procedure for thiazoles (3a-i) and Δ^4-thiazolines (6a,b).

To a stirred and ice-cooled solution of 1a-f (1 mmole) in dry and ethanol-free $CHCl_3$[10] (10 ml) a solution of freshly prepared 2a,b (1 mmole for 2a and 2 mmoles for 2b) in the same solvent (10 ml) was added dropwise under an atmosphere of nitrogen. When addition was complete the mixture was stirred for 15 min and then a slight excess of triethylamine in $CHCl_3$ (5 ml) was added dropwise under stirring. After

Table. Yields, mp, ir and ^{1}H nmr spectral data of thiazoles 3a-i and Δ^4-thiazolines 6a,b

Compd No	R	R'	X	Yield[a] (%)	Mp (°C)	Ir (KBr) (cm^{-1})	^{1}H Nmr ($CDCl_3$-DMSO-d_6) (δ)
3a	H	C_6H_5	H	65	207-9	3280 (N-H), 2200 (C≡N) 1605, 1555 (C=C, C=N)	6.7-8.2 (m, phenyl and amino H)
3b	H	C_6H_5	CF_3	55	183-4	3280 (N-H), 2210 (C≡N) 1620, 1570 (C=C, C=N)	6.7-8.4 (m, phenyl and amino H)
3c	H	C_6H_5	Cl	52	187-8	3290 (N-H), 2205 (C≡N) 1610, 1565 (C=C, C=N)	6.8-8.4 (m, phenyl and amino H)
3d	H	C_6H_5	CH_3	63	182-3	3290 (N-H), 2200 (C≡N) 1610, 1550 (C=C, C=N)	2.4 (s, methyl H), 6.7-8.1 (m, phenyl and amino H)
3e	H	C_6H_5	OCH_3	67	180-1	3280 (N-H), 2200 (C≡N) 1600, 1540 (C=C, C=N)	3.8 (s, methoxyl H), 6.6-7.9 (m, phenyl and amino H)
3f	H	C_6H_5	$N(CH_3)_2$	94	177-8	3300 (N-H), 2200 (C≡N) 1600, 1570 (C=C, C=N)	3.0 (s, dimethylamino H), 6.6-7.9 (m, phenyl and amino H)
3g	H	CH_3	H	59	186-8	3290 (N-H), 2200 (C≡N) 1610, 1520 (C=C, C=N)	3.1 (d,[b] methyl H, J=5 Hz), 7.4-8.0 (m, phenyl H), 7.8 (br, amino H, D_2O exchanged)
3h	H	CH_3	CF_3	61	196-8	3310 (N-H), 2200 (C≡N) 1620, 1560 (C=C, C=N)	3.1 (d,[b] methyl H, J=5 Hz), 7.7-8.1 (m, phenyl and amino H)
3i	H	CH_3	$N(CH_3)_2$	69	160-2	3300 (N-H), 2200 (C≡N) 1620, 1580 (C=C, C=N)	3.0 (s, dimethylamino H), 3.1 (d,[b] methyl H, J=5 Hz), 6.6-7.2 (m, phenyl and amino H)
6a	C_6H_5	C_6H_5	H	16	266-7	2200 (C≡N), 1622 1590, 1560 (C=C, C=N)	7.2-8.1 (m, phenyl H)
6b	C_6H_{11}	C_6H_5	H	10	217-9	2195 (C≡N), 1620 1575, 1560 (C=C, C=N)	1.1-1.9 (m, cyclohexyl H), 7.2-7.5 (m, phenyl H)

[a] Yields are based on starting enamines. [b] Doublet converted into a singlet upon treatment with D_2O.

keeping the resulting mixture at room temperature for 2 h, the solvent and the excess of triethylamine was evaporated under reduced pressure. Column chromatography of the residue gave thiazoles 3 along with unreacted starting enamines and mixtures of small amounts of unidentified by-products. Yields, mp and ir and ^{1}H nmr spectral data of thiazoles 3a-i are gathered in the Table. Thiazoles 3a,g were identical (mixed mp and superimposable ir spectra) with samples obtained by the Hantzsch's procedure given below.

Thiazolines 6a,b were obtained from enamines 1g,h and 2a following the above procedure. Their yields, mp, and ir and ^{1}H nmr spectral data are given in the Table.

Hantzsch's synthesis of thiazoles 3a,g.

A recent procedure [11] was employed. A solution of Br_2 (0.4 ml) in $CHCl_3$ (5 ml) was added during 10 min to a stirred solution of 1-cyanoacetophenone (1.5 g) in $CHCl_3$ (15 ml). After 45 min the solution was washed with aqueous Na_2CO_3, dried, and evaporated to give an oil (2.4 g) shown by ^{1}H nmr to contain 1-bromo-1-cyanoacetophenone (85%). Condensation of this oil with an equivalent amount of N-phenylthiourea gave the thiazole 3a (0.6 g; 38%). The thiazole 3g was similary obtained in a 35% yield from 1-bromo-1-cyanoacetophenone and N-methylthiourea.

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REFERENCES

1. A.Corsaro, U.Chiacchio and G.Purrello, J.Chem.Soc., Perkin Trans. I, 1977, 2154.
2. A.Corsaro, U.Chiacchio, A.Compagnini and G.Purrello, J.Chem.Soc., Perkin Trans. 1980, 1635.
3. A.Corsaro, M.Tarantello and G.Purrello, Tetrahedron letters, 1981, 3305.
4. A.Corsaro, A.Compagnini, M.Tarantello, S.Barbaro and G.Purrello, Synth.Commn., 1982, 12, 865.
5. A.Corsaro, U.Chiacchio, G.Perrini, P.Caramella and G.Purrello, J.Heterocyclic Chem., in the press.
6. G.Ottmann and H.Hooks, J.Org.Chem., 1966, 31, 838.
7. C.P.Joshua and K.N.Rajasekharan, Aust.J.Chem., 1977, 30, 563.
8. H.Oguru, S.Sugimoto and T.Hoh, Org.Mass Spectrom., 1970, 3, 1341.
9. A.R.Katritzky and C.W.Rees, 'Comprehensive Heterocyclic Chemistry', Pergamon, Oxforf, 1984, Part 4B, p.248.
10. A.I.Vogel,'Pratical Organic Chemistry', Italian Ed., Ambrosiana, Milano, 1967, p.178.
11. T.N.Birkinshaw, D.W.Gillon, S.A.Harkin, G.D.Meakins and M.D.Tirel, J.Chem.Soc., Perkin Trans I, 1984, 147.

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