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HETEROSUBSTITUTED ACETYLENES XXVII[1]

SYNTHESIS OF 4-AMINO-2-PYRIDONES BY THE REACTION OF YNAMINES WITH STYRYLISOCYANATES

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Abstract—Styrylisocyanates add to ynamines to give 4-amino-2 (1H) pyridones (III) by a 1,4-cycloaddition. Under the reaction conditions the 1:1-adducts (III) are further N-acylated with a second mole of syrylisocyanate to urea derivatives (IV). These decompose upon heating into the parent compounds.

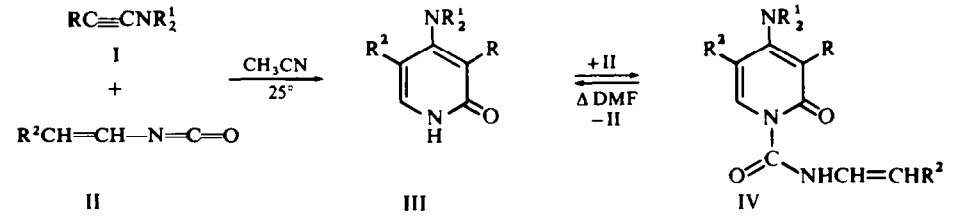
N-, and O-methylation of III as well as IR, UV and NMR spectra confirm the proposed structures of the 1:1- and 1:2-adducts III and IV.

YNAMINES as highly reactive nucleophilic acetylenes[2] are known to undergo facile cycloadditions to carbonyls,[3] imines,[3,4] and other isolated[5–9] conjugated or cumulated multiple bond systems.[4,9–13]

Amongst these; ynamines have been reacted with phenylisocyanate to give 4-amino-2-quinolones and 2-amino-4-quinolones depending on the reaction conditions.[4,13] This paper describes the reaction of ynamines with several styrylisocyanates prepared in this laboratory.[14]

When styrylisocyanate (II) is added to an ynamine (I) in ether or acetonitrile at room temperature, an exothermic reaction occurs and a 2:1-adduct precipitates almost immediately. Upon heating the 2:1 adduct dissociates into a 1:1-adduct and styrylisocyanate II.

Evidence will be given below that the 1:1-adduct results from a 1,4-cycloaddition of the ynamine to the vinylisocyanate with formation of a 4-amino-2 (1*H*) pyridone derivative (III). This 1:1-adduct (III) is further acylated with a second mole of styrylisocyanate to the 2:1-adduct (IV).



The structural assignment of III is based on classical conversion of pyridones[15–19] into the N-methyl-2-pyridone (V) and the O-methylpyridine (VII) via the chloropyridine (VI). The latter was further hydrogenated to the 4-aminopyridine (VIII) which displayed two NMR singlets at τ 1·68 and 1·80 downfield from the other aromatic proton signals.[20] The signal at τ 1·68 is enlarged due to a slight coupling with the Me group. This makes sure that III is a 4-amino-2-pyridone resulting from a 1,4-addition and not a 2-amino-4-pyridone which might have resulted from an initial 1,2-addition, subsequent opening of the 4-membered ring adduct and cyclization to the 2-amino-4-pyridone (compare Ref 4). Its corresponding 2-aminopyridine

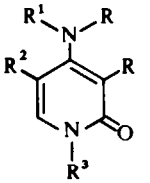


TABLE 1. IR AND UV DATA OF 4-AMINO-2-PYRIDONE DERIVATIVES

No.	R	R^1	R^2	R^3	IR μ (KBr) s: strong, m: medium, w: weak. CCl_4 when *. sh: shoulder, br: broad				UV λ_{max} mμ(ε.10^{-3}) in $CHCl_3$ or CH_3OH when*
					NH (mull C_4Cl_6)	C=O urea	C=O ring	C=C	
IIIa	Me	Et	Ph	H	3·02w, 3·17sh, 3·24sh	—	6·12s *6·11s	6·23sh, 6·54w	309(9·1) 256(16·9)
IIIb	Me	Et	*p*-$MeOC_6H_4$	H	3·04w, 3·21sh, 3·26sh	—	6·12s	6·32sh, 6·59m	310(9·5) 254(21·4)
IIIc	Ph	Me	Ph	H	3·08w, 3·21sh, 3·28sh	—	6·14s	6·24m, 6·41w	312(9·2) 255(21·0)* 315(9·3) 260(23·0)
IIId	Ph	Me	*p*-$MeOC_6H_4$	H	3·09w, 3·22br	—	6·15s	6·23sh, 6·39sh	318(8·6) 260(26·9)
V	Me	Et	Ph	CH_3	—	—	6·10s	6·26s, 6·54w	307(8·2) 253(14·8)* 309(8·5) 261(16·4)
IVa	Me	Et	Ph	CONHCH=CHPh	3·28br	5·82s	6·12s	6·31m, 6·60br	336(27·3) 266(22·6)
IVb	Me	Et	*p*-$MeOC_6H_4$	CONHCH=CHC_6H_4OMe*p*	3·4br	5·78s	6·1m	6·2m, 6·6br	341(27·3) 267(28·4)
IVc	Ph	Me	Ph	CONHCH=CHPh	3·27m, 3·32m	5·79s	6·11s	6·26m, 6·60br	332(26·9) 262(30·2)
IVd	Ph	Me	*p*-$MeOC_6H_4$	CONHCH=CHC_6H_4OMe*p*	3·33br	5·80s	6·10s	6·21s, 6·60br	341(32·4) 266(35·1)
IX	Me	Et	Ph	CONHPh	3·33br	5·74s *5·78s	6·19m *6·08m	6·23m, 6·60br	321(11·7) 254(20·7)

TABLE 2. IR AND UV DATA OF 4-AMINOPYRIDINE DERIVATIVES

No.	R	IR μ (KBr) C=C and C=N	UV a) CH_3OH b) $CHCl_3$ $\lambda_{max}^{m\mu}(\varepsilon \cdot 10^{-3})$
VI	Cl	6·12 w, 6·24 w, 6·32 w, 6·43 s	(a) 304 (4·1) 256 (11·8) 232 (12·8)
VII	OMe	6·24 w, 6·32 s, 6·43 m	(a) 284 (6·7 240 (15·7) (b) 284 (6·7) 243 (15·7)
VIII	H	6·24 w, 6·36 s	(a) 300 (3·5) 252 (7·8) 230 (8·2)

would have displayed an NMR singlet for the C-6 proton at $\tau \sim 1{\cdot}8$ and for the C-4 proton a singlet at $\tau \sim 2{\cdot}6$.[21]

The IR $\nu_{C=O}$ absorption at ~6·1 μ in all pyridones (III) as well as in the N-methylpyridone (V) show that III exist predominantly in the 2(1*H*)-pyridone form and not in the hydroxypyridine form.[15–19] This is further confirmed by UV spectrum of the methoxypyridine derivative (VII) which shows a hypsochromic shift of both maxima relative to the parent pyridones IIIa and V (Tables 1 and 2).

The 2:1-adducts (IV) show in addition to the CO absorption at ~6·1 μ attributed to the pyridone a second one at ~5·8 μ (Table 1) due to the CO group of the urea function. The position of this band is comparable to that at 5·7–5·8 μ observed in a series of N-acyl compounds where the nitrogen is part of an heterocycle.[22,23] Relative to the parent pyridones (III) a bathochromic shift is observed in the UV spectra of the acylated compounds (IV). These IR and UV data support the N-acylated structure (IV) of the 2:1-adducts and rule out O-acylation which has been encountered besides N-acylation in other cases.[24,25] The 4-aminopyridone (IIIa) can also be acylated with phenylisocyanate to IX. This reaction is reversible at the m.p. of IX (thermal cleavage of IV and IX with formation of isocyanate is not particular to either N- or O-acyl derivaties because both urea and carbamates are reported to undergo such a reaction[26]).

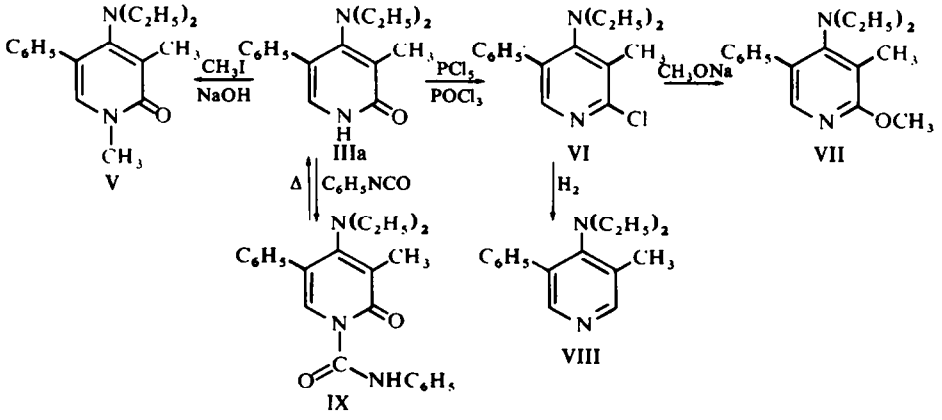


TABLE 3. ANALYTICAL DATA

No.	Yield %	m.p.† or b.p.	Formula (MW)	Calculated %				Found %			
				C	H	N	O	C	H	N	O
IIIa	84	232°[b]	$C_{16}H_{20}N_2O$ (256)	74·96	7·86	10·93	6·24	74·82	7·87	11·02	5·86
IIIb	80	232°[b]	$C_{17}H_{22}N_2O_2$ (286)	71·30	7·74	9·78	11·17	70·94	7·79	9·68	11·02
IIIc	58	250°[c]	$C_{19}H_{18}N_2O$ (290)	78·59	6·25	9.65	5.51	78·29	5·75	9·85	5·82
		240° with C_2H_5OH	$C_{21}H_{24}N_2O_2$ (336)	74·97	7·19	8·33	9·51	74·86	7·19	8·24	9·71
IIId	86	266°[d]	$C_{20}H_{20}N_2O_2$ (320)	74·97	6·29	8·74	9·99	74·62	6·24	8·92	10·23
V	95	96°[a]	$C_{17}H_{22}N_2O$ (270)	75·52	8·20	10·36	5·92	75·87	8·19	10·23	6·01
IVa	88	165°[a]	$C_{25}H_{27}N_3O_2$ (401)	74·78	6·78	10·47	7·97	74·86	6·75	10·47	8·03
IVb	70	154°[a]	$C_{27}H_{31}N_3O_4$ (461)	70·26	6·77	9·11	13·87	69·68	6·84	8·93	14·13
IVc	92	176°[f]	$C_{28}H_{25}N_3O_2$ (435)	77·22	5·79	9·65	7·35	77·34	6·11	9·37	7·18
IVd	62	200°[a]	$C_{30}H_{29}N_3O_4$ (495)	72·71	5·90	8·48	12·91	72·27	5·95	8·40	13·12
IX	99	165°[b]	$C_{23}H_{25}N_3O_2$ (375)	73·57	6·71	11·19	8·52	73·65	6·78	11·22	8·83
VI	75	150°/0·01 mm, ~80°	$C_{16}H_{19}N_2Cl$ (275)	69·93	6·97	10·20	12·90*	69·91	6·79	10·22	12·83*
VII	84	~125°/0·01 mm	$C_{17}H_{22}N_2O$ (270)	75·52	8·20	10·36	5·92	75·04	7·73	10·35	5·91

* % of chlorine.

† recrystallized from: [a] chloroform-acetone-pet. ether 40–60; [b] chloroform-acetone; [c] dimethylformamide; [d] dimethylformamide-acetone; [e] hexane; [f] acetone-light petroleum 40–60.

EXPERIMENTAL

Technical assistance of Mr. M. A. Hartemink.

M.ps and b.ps are uncorrected. IR spectra were taken as KBr pellets with a Perkin-Elmer model 21 double-beam instrument, UV spectra with a Cary recording spectrophotometer model 14 and NMR spectra on a Varian A-60 instrument, using TMS as an internal standard. Analytical data are given in Table 3. Elemental analyses carried out by Mr. F. Goes of this laboratory.

N-*styrylcarbamyl-2 pyridones* (IV) *from ynamines* (I) *and styrylisocyanates* (II). To a soln of 0·02 mole of I in 10 ml solvent [ether for I ($R = Me$, $R^1 = Et$) acetonitrile for I, $R = Ph$, $R^1 = Me$] was added dropwise 0·04 mole of II in 10 ml of the same solvent. The collected ppt was the almost pure 2:1-adduct IV. Solvents of cryatallization, yields and analytical data are listed in Table 3.

To avoid the oligomerization of II on standing, the parent azide should be thermolysed by heating under reflux for 30 min in light petroleum 100–120. This soln was then added dropwise to a soln of I in the appropriate solvent.

4-*Amino-2-pyridones* III *from* N-*styrylcarbamyl-2-pyridones* IV. Compound IV (0·02 mole) in 20 ml DMF was heated under reflux for 2 hr. Then 20 ml acetone were added to the cooled mixture and normally the pyridones III crystallized (Table 3).

When the adducts IV were heated at 180° under high vacuum (0·01 Torr) in a 3-bulb tube a liqud distilled slowly as well as a solid. When the liquid was redistilled at ~130°/12 mm pure styrylisocyanate was collected and identified by IR.

N-*styrylcarbamyl-2 pyridone* IVa *from* 4-*diethylamino-2-pyridone* IIIa *and styrylisocyanate* (II, $R^2 = Ph$). A soln of 0·256 g (0·001 mole) of IIIa and 0·15 g of II ($R^2 = Ph$) in 3 ml $CHCl_3$ and a trace of dry HCl was kept at room temp overnight. Then 3 ml acetone were added and the 2:1-adduct IVa precipitated (0·28 g, 70% yield). IVa was identical with the adduct prepared directly from 1-diethylamino-1-propyne and styrylisocyanate.

4-*Diethylamino-3-methyl-5-phenyl-1-phenylcarbamyl-2 pyridone* IX. A soln of 3 g (0·0115 mole) of IIIa and phenylisocyanate 1·5 g (0·0126 mole) in 5 ml $CHCl_3$ and a trace of dry HCl was heated for 3 hr under reflux. Acetone was then added and pure IX crystallized; 4·3 g, yield 99% (Table 3).

4-*Diethylamino*-1,3-*dimethyl-5-phenyl-2-pyridone* V[27]. A soln of 0·6 g NaOH in 4 ml water was added dropwise to a refluxing suspension of 1 g (0·0039 mole) of IIIa in 7 ml MeOH and 3·2 g MeI. After 1 hr refluxing 1·6 g MeI and 0·3 g NaOH were dissolved in 2 ml water and added. After refluxing for another hr, the MeOH was evaporated *in vacuo*. The alkaline residue was twice extracted with $CHCl_3$, the extract dried with Na_2SO_4 and evaporated. The residue was crystallized from hexane giving 1 g (95% yield) of pure VI (Table 3).

2-*Chloro*-4-*diethylamino*-3-*methyl*-5-*phenylpyridine* VI[28]. A mixture of 2·5 g (0·01 M) of IIIa, 5 ml of $POCl_3$ and 1 g PCl_5 was heated for 2 hr at 115°; it was then cooled and poured onto crushed ice, neutralized with NaOH aq and extracted with ether. The ether extracts were dried, concentrated, and the residue distilled in a 3-bulb tube, b.p. ~150° (0·01 mm). The distillate 2 g (yield: 75%) solidified as almost pure VI.

4-*Diethylamino*-2-*methoxy*-3-*methyl*-5-*phenylpyridine* VII (according to Ref. 16). Chloropyridine VI (1·7 g) and NaOMe (from 0·8 g Na) in 5 ml MeOH were refluxed for 20 hr. Neutralization with methanolic HCl, removal of the NaCl, evaporation and distillation gave VIII, b.p. ~125° (0·05 mm) contaiminated with some 15% of starting material (GLC). It was purified by column chromatography over silicagel and eluted with hexane–ether (4–1) 1·4 g (yield: 84%) (Table 3).

4-*Diethylamino*-3-*methyl*-5-*phenylpyridine* VIII. 0·06 g of chloropyridine VI dissolved in 5 ml of EtOH was hydrogenated over Adam's platinum at room temp and press. When one mole equiv of H_2 had been taken up, the soln was filtered, the solvent evaporated to dryness, water added to the residue and the soln neutralized with $NaHCO_3$ and extracted with ether. This ethereal soln was dried over Na_2SO_4 and the ether evaporated. The oily residue was 95% pure VIII (5% starting VI by VPC). It was distilled at 110°/0·05 Torr. NMR $CDCl_3$ τ[H]m: 1·68[1]s, 1·80[1]s, 2·6[1]m, 7·15[4]q, 7·72[3]s, 9·06[6]t.

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