Reaction of α-Ketoketene *S,N*-Acetals with Hydroxylamine: A Facile General Route to 5-Aryl-3-(*N*-arylamino, *N*-alkylamino, or *N*-azacycloalkyl)-isoxazoles[1]

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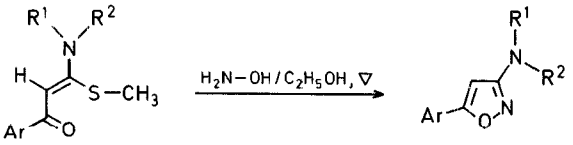
In the course of our synthetic studies on polarized ketene *S,S*-, *S,N*-, and *N,N*-acetals, we have developed simple and convenient routes for *N*-alkyl(or aryl)-aminopyrazoles[2], -pyrimidines[3], and the corresponding -pyridones[4]. As part of this investigation, we now report a facile general method for 5-aryl-3-*N*-arylamino-(or -alkylamino or -azacycloalkyl)-isoxazoles **2** by reacting **1** with hydroxylamine. Our survey of the literature revealed that the doubly activated ketene *S,N*-acetal derived from acetylacetone has been reacted[5] with hydroxylamine to give the corresponding 3-anilinoisoxazole. However, no attempts to develop a general synthetic route for 3-*N*-substituted-aminoisoxazoles from the easily available ketoketene *S,N*-acetals **1** have been made.



1 **2**

Table. 5-Aryl-3-(*N*-substituted-amino)-isoxazoles **2a–o** prepared

Product No.	Ar	R^1	R^2	Yield [%]	m.p. [°C]	Molecular formula[a] or Lit. m.p. [°C]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$ or $CDCl_3$/DMSO-d_6) δ [ppm]	M.S. *m/e* (M^+)
2a	C_6H_5	C_6H_5	H	88	143–144°	142–143°[5]	3340, 1620, 1600	6.25 (s, 1H, H-4); 6.7–7.85 (m, 10 H_{arom}); 8.0 (br. s, 1H, exchangeable with D_2O, NH)	236
2b	4-H_3C—C_6H_4	C_6H_5	H	80	186°	$C_{16}H_{14}N_2O$ (250.3)	3380, 1625, 1600	2.31 (s, 3H, CH_3); 6.28 (s, 1H, H-4); 6.7–7.7 (m, 4 H_{arom}); 8.3 (m, 5 H_{arom}); 8.30 (br. s, 1H, exchangeable with D_2O, NH)	250
2c	4-H_3CO—C_6H_4	C_6H_5	H	75	174°	$C_{16}H_{14}N_2O_2$ (266.3)	3410, 1624, 1602	3.78 (s, 3H, OCH_3); 6.22 (s, 1H, H-4); 6.7–7.5 (m, 9 H_{arom} + NH)	—
2d	4-Cl—C_6H_4	C_6H_5	H	85	194°	$C_{15}H_{11}ClN_2O$ (270.5)	3400, 1625, 1600	6.30 (s, 1H, H-4); 6.75–7.8 (m, 9 H_{arom}); 8.62 (br. s, 1H, exchangeable with D_2O, NH)	272, 270
2e	C_6H_5	C_2H_5	H	75	101°	$C_{11}H_{12}N_2O$ (188.2)	3265, 1625, 1600	1.22 (t, 3H, CH_3); 3.25 (br. q, 2H, CH_2); 3.98 (br. s, 1H, NH); 5.86 (s, 1H, H-4); 7.15–7.5 (m, 3 H_{arom}); 7.5–7.8 (m, 2 H_{arom})	—
2f	4-H_3CO—C_6H_4	C_2H_5	H	69	78–80°	$C_{12}H_{14}N_2O_2$ (218.3)	3275, 1628, 1600	1.21 (t, 3H, CH_3); 3.22 (q, 2H, CH_2); 3.70 (s, 3H, OCH_3); 3.78 (br. s, 1H, NH); 5.80 (s, 1H, H-4); 6.6–7.7 (m, 4 H_{arom})	—
2g	4-Cl—C_6H_4	C_2H_5	H	92	141°	$C_{11}H_{11}ClN_2O$ (222.5)	3280, 1628, 1600	1.21 (t, 3H, CH_3); 3.25 (br. q, 2H, CH_2); 3.75 (br. s, 1H, NH); 5.81 (s, 1H, H-4); 7.2–7.7 (m, 4 H_{arom})	—
2h	C_6H_5	$C_6H_5CH_2$	H	56	136°	$C_{16}H_{14}N_2O$ (250.3)	3300, 1622	4.35 (br. s, 3H, CH_2 + NH); 5.92 (s, 1H, H-4); 7.1–7.45 (m, 8 H_{arom}); 7.4–7.75 (m, 2 H_{arom})	—
2i	4-Cl—C_6H_4	$C_6H_5CH_2$	H	86	116°	$C_{16}H_{13}ClN_2O$ (284.5)	3320, 1630	4.30 (br. s, 3H, CH_2 + NH); 5.90 (s, 1H, H-4); 7.1–7.5 (m, 7 H_{arom}); 7.5–7.7 (m, 2 H_{arom})	286, 284
2j	4-H_3C—C_6H_4	$C_6H_5CH_2$	H	92	121°	$C_{17}H_{16}N_2O$ (264.3)	3320, 1630	2.32 (s, 3H, CH_3); 4.20 (br. s, 1H, NH); 4.35 (br. s, 2H, CH_2); 5.91 (s, 1H, H-4); 7.05–7.4 (m, 7 H_{arom}); 7.4–7.7 (m, 2 H_{arom})	—
2k	C_6H_5	—$(CH_2)_4$—		90	95°	$C_{13}H_{14}N_2O$ (214.3)	1630, 1610, 1595	1.8–2.2 (m, 4H, CH_2); 3.2–3.5 (m, 4H, CH_2); 5.95 (s, 1H, H-4); 7.2–7.5 (m, 3 H_{arom}); 7.5–7.8 (m, 2 H_{arom})	—
2l	C_6H_5	—$(CH_2)_5$—		88	85°	$C_{14}H_{16}N_2O$ (228.3)	1620, 1595, 1580	1.5–1.75 (m, 6H, CH_2); 3.1–3.3 (m, 4H, CH_2); 5.98 (s, 1H, H-4); 7.2–7.4 (m, 3 H_{arom}); 7.5–7.7 (m, 2 H_{arom})	—
2m	C_6H_5	—$(CH_2)_2$—O—$(CH_2)_2$—		87	155°	$C_{13}H_{14}N_2O_2$ (230.3)	1625, 1595, 1550	3.2–3.4 (m, 4H, CH_2); 3.65–3.9 (m, 4H, CH_2); 6.08 (s, 1H, H-4); 7.25–7.5 (m, 3 H_{arom}); 7.6–7.8 (m, 2 H_{arom})	—
2n	C_6H_5	$-(CH_2)_2-N(C_6H_5)-(CH_2)_2-$		88	127°	$C_{19}H_{19}N_3O$ (309.4)	1625, 1595, 1545	2.2–2.65 (m, 8H, CH_2); 6.18 (s, 1H, H-4); 6.95–7.5 (m, 8 H_{arom}); 7.5–7.85 (m, 2 H_{arom})	

[a] Satisfactory microanalyses obtained: C ±0.39, H ±0.33, N ±0.34.

When **1a** was refluxed with hydroxylamine (generated *in situ*) in ethanol, corresponding 3-anilinoisoxazole **2a** was obtained in 88% yield. The other 3-anilino- **(2b–d)**, 3-ethylamino- **(2e–g)**, and 3-benzylaminoisoxazoles **(2h–j)** were similarly obtained in 56–92% yields. The corresponding *S,N*-acetals **1k–n**, derived from secondary amines, similarly yielded the corresponding isoxazoles **2k–n** in 87–90% yields (Table).

Very few 3-*N*-substituted-aminoisoxazoles have been reported in the literature. The only known 5-phenyl-3-anilino-(or *p*-bromoanilino)-isoxazoles were prepared by reaction of hydroxylamine with either phenylpropiolthioanilide[6,7] or benzoyl ketene *O,N*-acetal[8]. The starting materials are not easily available in both the methods and the yield of isoxazole is low in the former case. The present method therefore provides a simple and high yield method for **2** from the easily available *S,N*-acetals **1**.

The *S,N*-acetals **1a–j** were prepared by our earlier reported procedure[3], while the cyclic *S,N*-acetals **1k–n** were obtained by methylation of the corresponding thioamides in the presence of potassium carbonate in refluxing acetone[9].

5-Aryl-3-*N*-arylamino-(or -alkylamino or -azacycloalkyl)-isoxazoles; General Procedure:

A solution of *S,N*-acetal **1a–n** (0.01 mol) and hydroxylamine (generated from 0.04 mol of hydroxylamine hydrochloride and 0.04 mol of potassium hydroxide in 5 ml of water, neutral to litmus) in ethanol (25 ml) is refluxed for 3–4 h. The ethanol is removed on a water bath and the concentrated reaction mixture is poured into ice-cold water (150 ml). The water layer is extracted with chloroform (2 × 75 ml), and the chloroform layer is dried with sodium sulfate, and evaporated to give isoxazoles **2a–n** which are crystallised from ethanol (Table).

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