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Synthesis of Heterocyclic Ketene N,O-acetals from 5(2H)-Isoxazolones

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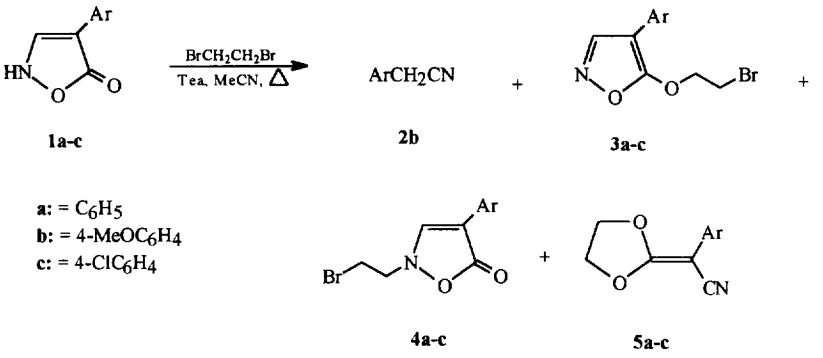
Abstract: Starting from 4-aryl isoxazolin-5-ones 1, a new synthesis of heterocyclic ketene N,O-acetals is described. © 1997 Elsevier Science Ltd.

While heterocyclic ketene aminals are versatile starting materials for the synthesis of fused heterocycles and their synthesis have received much attention, the synthesis of the corresponding heterocyclic N,O-acetals has only been studied in a few cases.[1-5] Continuing our researches on the reactivity of the 5(2H)-isoxazolones as nucleophiles [6,7] and bearing in mind the reported mechanism of the basic ring opening of the 3-unsubstituted 2-isoxazolin-5-ones,[8] we have considered the application of this process to the preparation of heterocyclic ketene N,O-acetals by basic ring opening and recyclization of isoxazolones of formula **4**.

The reaction of the known 4-aryl-isoxazolin-5-ones **1 a-c** with 1,2-dibromoethane, in acetonitrile and in the presence of one equivalent of triethylamine, gave a mixture of products which were separated by chromatography (see experimental). In all cases the major product was the N-alkylated derivative **4** (Scheme 1 and Table 1).

The arylacetonitrile **2b,** which was isolated in only one case, arises from the ring cleavage of the starting isoxazolone **1b** followed by decarboxylation.[9] In all cases we obtained a low yield of the O-alkylated products **3 a-c** besides the ketene acetals **5 a-c**. These compounds arise from the compounds **3** on the reaction with triethylamine, as demonstrated in a separate reaction (Scheme 2).

Scheme 1

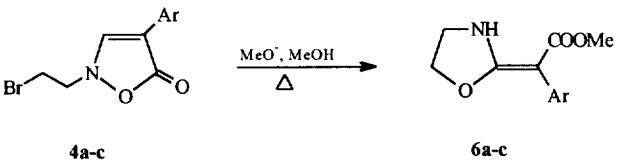


The treatment of the N-alkylated derivatives **4** with sodium methoxide in boiling methanol, gave the ketene N,O-acetals **6** in very good yield (Scheme 3 and Table 1).

Scheme 2

The E stereochemistry of compounds **6** is suggested by the downfield shift (δ = 8.32-8.39 ppm) of the NH signal in the ^{1}H-nmr spectra,owing intramolecular hydrogen bond formation.[3] Definitive confirmation of the structure follows from X-ray diffraction analysis[10]. The Figure shows the ORTEP of the compound **6b** with the atomic numbering scheme of the heavy atoms.

Scheme 3



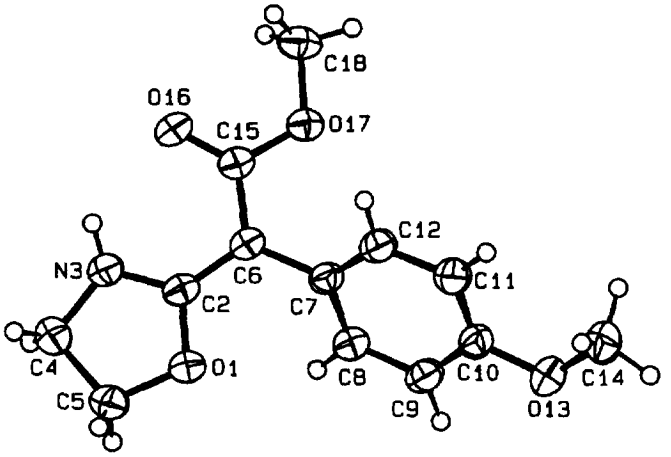
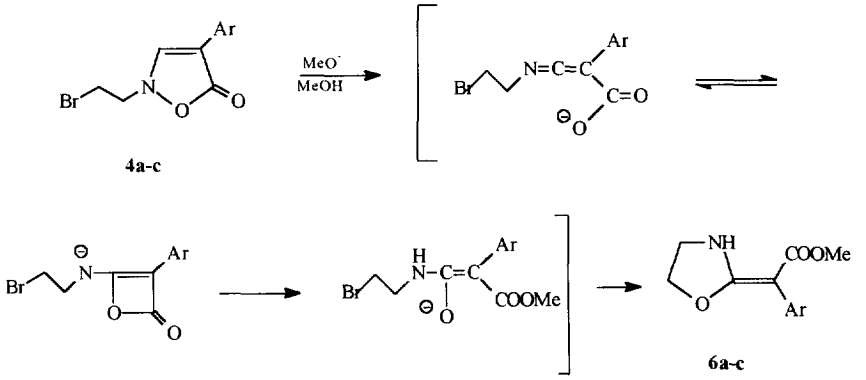


Figure: ORTEP[11] plot of **6b**. Atomic displacement parameters at 50% of probability level. H atoms not to scale.

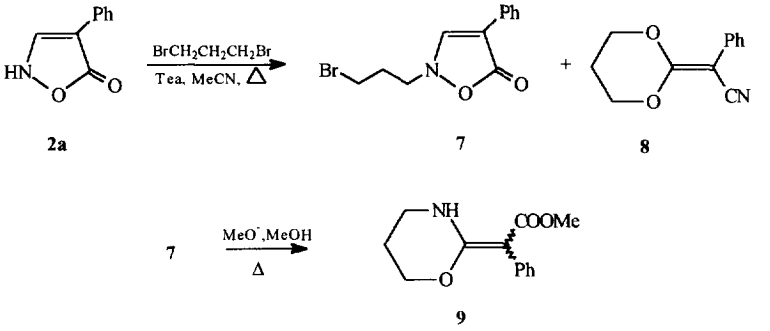
The mechanism for the formation of compounds **6**, which shows analogies with the mechanism reported in ref.8, is depicted in Scheme 4.

Scheme 4



Sodium methoxide hydrogen abstraction forms a keteneimine intermediate which cyclizes to a four-membered ring intermediate. This latter rearranges to the final products by methoxide attack to the carbonyl group and nucleophilic displacement of the bromine atom by the negative oxygen. From compound **1a**, with 1,3-dibromopropane and following the previously reported reaction pathway, the N-alkylated product **7** and minor amount of the ketene acetal **8** were obtained. Compound **7**, on reaction with sodium methoxide in methanol, afforded excellent yield of the ketene N,O-acetal **9**, as E/Z mixture (Scheme 5 and Table 1).

Scheme 5



Spectral data are collected in Table 2. The easy route to compounds **6** represents an useful addition to the group of synthons for heterocyclic synthesis.

EXPERIMENTAL

Melting points were determined on a Buchi apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 298 instrument, in nujol mull for solids and as liquid film for oils. ^{1}H-NMR were recorded on a Varian Gemini 200 spectrometer in $CDCl_3$ solution unless otherwise stated. Column Chromatography was performed on Kieselgel Merck 60,0.063-0.2 mm. Evaporation was carried out under vacuum in a rotary evaporator. Sodium sulfate was used as drying agent.

Compounds **1a** [9], **1b** [12] and **1c** [12] were prepared according to the literature procedure.

*Reaction of 5(2H)-isoxazolones **1** with 1,2-dibromoethane. General Procedure.*

The 5(2H)-isoxazolone **1** (20 mmol) was dissolved in CH_3CN (50 mL) and then triethylamine (2.8 mL, 20 mmol) and 1,2 dibromoethane (5.17 mL, 60 mmol) were added. The mixture was refluxed for 1h. After evaporation of the solvent, water (50 mL) was added and the mixture extracted with CH_2Cl_2 (2 x 50 mL). The organic layer was dried, filtered and evaporated. The residue was purified by column chromatography (eluent n-pentane-Et_2O, 1:3). The products were crystallized from Et_2O-hexane (Table 1)

*Synthesis of [1,3]Dioxolan-2-ylidene-aryl-acetonitriles **5** from Compounds 3.General Procedure.*

The compound **3** (2 mmol) was dissolved in CH_3CN (20 mL) and then triethylamine (0.55 mL, 4 mmol) was added. The mixture was refluxed for 1h. After evaporation of the solvent, water (20 mL) was

added and the mixture extracted with CH_2Cl_2 (2 x 20 mL). The organic layer was dried, filtered, evaporated and crystallized (Table 1).

*Synthesis of Oxazolidin-2-ylidene-aryl-acetic acid methyl esters **6** from Compounds **4**. General Procedure.*

The compound **4** (4 mmol) was dissolved in MeOH (50 mL) and then a solution of Na (115 mg, 5 mmol) in MeOH (5 mL) was added. The solution was refluxed for 10 min. After evaporation of the solvent, water (30 mL) was added and the mixture extracted with CH_2Cl_2 (2 x 30 mL). The organic layer was dried, filtered, evaporated and crystallized (Table 1).

*Reaction of the 5(2H)-isoxazolone **1a** with 1,3-dibromopropane. Synthesis of Compounds 7 and 8.*

The compound **1a** (3.22 g, 20 mmol) was dissolved in CH_3CN (60 mL) and then triethylamine (2,8 mL, 20 mmol) and 1,3-dibromopropane (6.1 mL, 60 mmol) were added. The mixture was refluxed for 1h. After evaporation of the solvent, water (50 mL) was added and the mixture extracted with CH_2Cl_2 (2 x 40 mL). The organic layer was dried, filtered and evaporated. The residue was purified by column chromatography (eluent CH_2Cl_2-Et_2O, 50 : 1) giving pure compounds **7** and **8** (Table 1).

*Synthesis of [1,3]Oxazinan-2-ylidene-phenyl-acetic acid methyl ester **9** from Compound 7.*

The compound 7 (1.13 g, 4 mmol) was dissolved in MeOH (50 mL) and then a solution of Na (115 mg, 5 mmol) in MeOH (5 mL) was added. The solution was refluxed for 5 min. After evaporation of the solvent, water (30 mL) was added and the mixture extracted with CH_2Cl_2 (2 x 20 mL). The organic layer was dried, filtered, evaporated and crystallized (Table 1).

*X-ray structure determination of **6b**.*

$C_{13}H_{15}NO_4$, F_w =249.27, triclinic setting, space group $P\bar{1}$, a = 7.081(1), b = 7.501(1), a = 13.153(2) Å, α = 82.34(1), β = 76.14(1), γ = 64.07(1) °, V = 609.7(2) Å^3, Z = 2, D_{cal} = 1.358 g.cm^{-3}, colourless, crystal dimension 0.30x0.25x020 mm^3, Siemens-P4 diffractometer, graphite monochromator, $K\alpha$ radiation (λ = 0.71069 Å), data collection: 3.2 < 2θ < 55 °, *hkl* range 0,9; -6,9; -16,17, No. of independent data 2360, 2022 observed [$I > 2\sigma(I)$]. The structure was solved by SIR92[13] and refined by full-matrix least-squares based on F by SDP[14] . Anisotropic heavy atoms, isotropic H atoms. Final R = 0.031, R_w = 0.039, $|\Delta\rho|_{max}$ = 0.16 e.Å^{-3}, Δ/σ_{max} = 0.01.

Table 1. New Compounds Prepared

Starting material	Product[a]	Yield (%)	mp (°C) (solvent)[b]
1a	**3a**	8	oil
	4a	56	107-108 (Et_2O)
	5a	20	63-64 (Et_2O-Hx)
1b	**2b**	24	oil
	3b	4	74-75 (Et_2O)
	4b	40	115-116 (Et_2O)
	5b	6	123-124 (Et_2O)
1c	**3c**	7	100-101 (Et_2O-Hx)
	4c	50	104-105 (Et_2O)
	5c	8	128-129 (Et_2O)
3a	**5a**	88	
3b	**5b**	85	
3c	**5c**	95	
4a	**6a**	73	137-138 (CH_2Cl_2-Et_2O)
4b	**6b**	85	130-131 (CH_2Cl_2-Et_2O)
4c	**6c**	90	186-187 (CH_2Cl_2-Et_2O)
1a	**7**	57	101-102 (CH_2Cl_2-Et_2O)
	8	10	89-90 (Et_2O)
7	**9**	71	122-123 (CH_2Cl_2-Et_2O)

[a] Satisfactory microanalyses obtained : C ± 0.20, H ± 0.13, N ± 0.14. [b] Hx : hexane.

Table 2. IR and ^{1}H-NMR Data of New Compounds.

Compd.	IR (nujol) ν cm^{-1}	1H-NMR ($CDCl_3$/TMS), δ, J (Hz)
3a	1643, 1635, 1605	3.70(2H,t,6.1),4.76(2H,t,6.1),7.24(1H,m),7.38 (2H,m),7.54(2H,m),8.44(1H,s)
3b	1655, 1614	3.69(2H,t,6.1), 3.81(3H,s), 4.74(2H,t,6.1), 6.92 (2H,d,8.8), 7.46(2H,d,8.8), 8.38(1H,s)
3c	1624, 1610	3.72(2H,t,6.1), 4.79(2H,t,6.1), 7.36(2H,d,8.7), 7.49(2H,d,8.7), 8.43(1H,s)
4a	1700, 1613, 1590	3.62(2H,t,5.8), 4.10(2H,t,5.8), 7.26(1H,m), 7.37 (2H,m), 7.71(2H,m), 8.13(1H,s)
4b	1692, 1591	3.62(2H,t,5.9), 3.82(3H,s), 4.06(2H,t,5.9), 6.93 (2H,d,8.8), 7.68(2H,d,8.8), 8.04(1H,s)
4c	1693, 1600	3.64(2H,t,5.8), 4.14(2H,t,5.8), 7.34(2H,d,8.7), 7.68(2H,d,8.7), 8.15(1H,s)
5a	2211,1631	4.58(2H,m), 4.66(2H,m), 7.15(1H,m), 7.31(2H, m), 7.52(2H,m)
5b	2212, 1632	3.78(3H,s), 4.59(4H,m), 6.86(2H,d,8.9), 7.43 (2H,d,8.9)
5c	2201, 1618	4.66(4H,m), 7.28(2H,d,8.8), 7.47(2H,d,8.8)
6a	3350, 1660, 1580	3.64(3H,s), 3.75(2H,t,7.8), 4.41(2H,t,7.8), 7.29 (5H,m), 8.36(1H,bs)[a]
6b	3320, 1662, 1590	3.65(3H,s), 3.75(2H,m), 3.80(3H,s), 4.42(2H,t,7.5), 6.86(2H,d,8.8), 7.18(2H,d,8.8), 8.32(1H,bs)[a]
6c	3315, 1645	3.65(3H,s), 3.77(2H,t,7.8), 4.43(2H,t,7.8), 7.25 (4H,m), 8.39(1H,bs)[a]
7	1696, 1610, 1584	2.32(2H,m), 3.49(2H,t,6.3), 3.89(2H,t,6.3), 7.25 (1H,m), 7.36(2H,m), 7.71(2H,m), 8.10(1H,s)
8	2200, 1603	2.27(2H,m), 4.43(4H,m), 7.14(1H,m), 7.28(2H, m), 7.49(2H,m)
9	3200, 3150,1640, 1580	E isomer : 2.04(2H,m), 3.46(2H,m), 3.59(3H,s), 4.18 (2H,m), 7.26(5H,m), 9.83(1H,s)[a] Z isomer : 1.88(2H,m), 3.46(2H,m), 3.74(3H,s), 4.18 (2H,m), 4.49(1H,s)[a], 7.26(5H,m)

[a] Exchange with D_2O

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