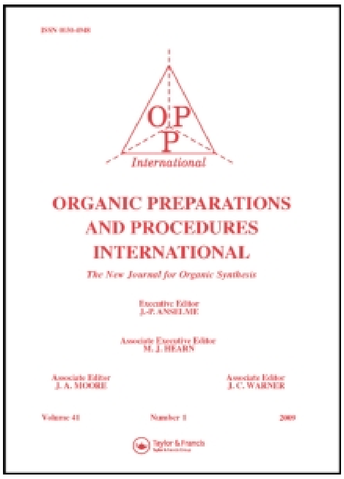

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SYNTHESIS OF UNUSUAL CONJUGATED AZOALKENES

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SYNTHESIS OF UNUSUAL CONJUGATED AZOALKENES†

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Conjugated azoalkenes are interesting products and useful in C-functionalizations,[1,2] as well as for the preparation of a number of five- (i.e., pyrroles, pyrrolines)[1,3] and six-membered heterocycles (i.e., pyridazines).[1] However, in spite of their considerable synthetic potential, their extremely variable stability and reactivity[1] have hindered the preparation and utilization of new classes of these derivatives, since each additional class required the thorough investigation of the most suitable reaction and work-up procedures. These facts have prompted us to amplify and diversify as much as possible the structures of conjugated azoalkenes by varying the functional groups linked to the azo-ene system.[1,4] Our previous investigations focussed on the substituents of the parent hydrazines which are precursors of hydrazones (1) from which the azo-system is derived in conjugated azoalkenes.[1,4] The present study significantly extends the variety of groups present on the precursor carbonyl compounds.

Halogenation of β-ketoamides, β-ketosulfones and β-ketophosphones followed by basic dehydrohalogenation in situ, provided new and interesting conjugated azoalkenes. In accordance with previous findings on analogous reactions, phenyltrimethylammonium tribromide (PTAB) was confirmed to be a highly specific brominating agent for carbon atoms in the α-position to the carbonyl group.[1,4,5] Tetra-*n*-butylammonium tribromide and pyridinium bromide perbromide gave less satisfactory results.

$$\underset{\mathbf{1}}{R_1NH\text{-}N{=}\underset{\substack{|\\R_2}}{C}CH_2R_3} \xrightarrow[\text{-HBr}]{\text{PTAB}} \underset{\mathbf{2}}{R_1N{=}N\text{-}\underset{\substack{|\\R_2}}{C}{=}CHR_3}$$

R_1 = phenyl, 3-nitro-2-pyridyl, 2-benzothiazolyl; R_2 = Me, Ph;
R_3 = $CONEt_2$, CONHPh, $CONHC_6H_4$-p-Cl, $CONHC_6H_4$-p-OMe, $PO(OMe)_2$, SO_2Me, $SO_2C_6H_4$-p-Me

The methodology for obtaining conjugated azoalkenes (2) as well as the physical properties and the spectral data, vary rather frequently from case to case. However, under suitable experimental conditions, the above-mentioned compounds were produced as mixtures of isomers in good to excellent yield and could be stored as pure red products, without special caution at ambient temperature. They showed no appreciable decomposition for several months, with the exceptions of 2c and 2h, which required storage in the refrigerator (at -20°), under nitrogen, protected from light; under these conditions, even 2c and 2h exhibited considerable stability for several weeks.

Table 1. Yield of Azoalkenes (**2**) from Hydrazones (**1**)[a]

Product (2)	R_1	R_2	R_3	PTAB	Time[b,c] (hrs)	Yield[e] (%)
2a	Ph	Me	$CONEt_2$	1.3	0.5	55
2b	Ph	Ph	CONHPh	1.7	0.5[d]	84
2c	Ph	Me	$PO(OMe)_2$	1.5	0.5	70
2d	Ph	Me	$SO_2C_6H_4$-p-Me	2.0	12.0	85
2e	3-nitro-2-pyridyl	Ph	CONHPh	1.5	0.5	50
2f	3-nitro-2-pyridyl	Me	$CONHC_6H_4$-p-Cl	1.0	0.5	78
2g	3-nitro-2-pyridyl	Me	$CONHC_6H_4$-p-OMe	2.5	0.5	51
2h	3-nitro-2-pyridyl	Me	$PO(OMe)_2$	1.5	0.5	57
2i	3-nitro-2-pyridyl	Me	SO_2Me	2.0	12.0	76[f]
2j	3-nitro-2-pyridyl	Me	$SO_2C_6H_4$-p-Me	2.0	12.0	68[f]
2k	2-benzothiazolyl	Me	$CONHC_6H_4$-p-Cl	1.6	0.5	74
2l	2-benzothiazolyl	Me	$CONHC_6H_4$-p-OMe	1.7	0.5	67

a) Solvent is THF and temperature is -20° unless otherwise noted. b) Time of bromination. c) The time of dehydrobromination is 15 min unless otherwise noted. d) The time of dehydrobromination is 24 hrs. e) Yield of pure isolated product. f) Carried out in CH_2Cl_2 at room temperature.

EXPERIMENTAL SECTION

Azoalkenes (2). General Procedure.- The hydrazones (prepared by well known techniques[4,6]) 1a-h, 1k and 1l (1 mmol) were dissolved in tetrahydrofuran (20 ml) at -20°, or in methylene chloride (20 ml) at room temperature in the case of 1i and 1j. To this stirred solution, was slowly added (30 min) PTAB in the molar ratio reported in Table 1. The reaction mixture was generally allowed to stand for a further 30 min, or 12 hrs in the case of 1d, 1i and 1j in the above-mentioned conditions. The mixture was then poured into a separatory funnel containing 50 ml of

Table 2. Physical and Spectral Properties of Azoalkenes (2)

Product (2)	mp[a] (°C)	IR ν (cm^{-1})	^1H-NMR (60 MHz)[d] δ (ppm)
2a	oil	1643 1575[b]	1.23 (t, 6H, 2 Et); 2.18 (s, 3H, Me); 3.13-3.73 (m, 4H, 2 Et); 7.00-7.16 (m, 1H, CH); 7.28-7.93 (m, 5H, Ar)[e]
2b	182-184	3400 1708, 1600[c]	7.05-8.43 (m, 17H, CH and Ar and NH, 1H, D_2O exchange)[e]
2c	oil	1620 1575 1260 1235 1030[b]	2.23 (d, 3H, $^4J_{PH}$=3 Hz, Me); 3.76 (s, 3H, OMe); 3.93 (s, 3H, OMe); 6.63 (d, 1H, $^2J_{PH}$=14 Hz, CH); 7.40-7.97 (m, 5H, Ar)[e]
2d	141-143	1615, 1570 1320 1145, 835[c]	2.40 (s, 3H, Me); 2.43 (s, 3H, Me); 7.17-8.00 (m, 10H, CH and Ar)[e]
2e	162-164	3310 1645 1590, 1535 1360[c]	6.83-7.00 (m, 12H, CH and Ar and pyridyl); 8.46-9.03 (m, 2H, pyridyl); 10.36 (br. s, 1H, NH, D_2O exchange)[f]
2f	163-165	3220, 3175 1660, 1610 1590, 1540 1310 830[c]	2.47 (s, 3H, Me); 7.26-8.26 (m, 6H, CH and Ar and pyridyl); 8.78-9.36 (m, 2H, pyridyl); 11.00 (br. s, 1H, NH, D_2O exchange)[f]
2g	133-135	3200, 3120 1690, 1605 1535 1365, 1300 1245	2.16 (s, 3H, Me); 3.78 (s, 3H, OMe); 6.53-7.80 (m, 6H, CH and Ar and pyridyl); 8.16-8.93 (m, 2H, pyridyl); 10.70 (br. s, 1H, NH, D_2O

Table 2 (continued)

		825^c	exchange)[e]
2h	98-100	1590, 1535, 1355, 1230, 1035^c	2.35 (d, 3H, $^4J_{PH}$=3 Hz, Me); 3.75 (s, 3H, OMe); 3.90 (s, 3H, OMe); 6.88 (d, 1H, $^2J_{PH}$=13 Hz, CH); 7.43-7.77 and 8.27-8.53 and 8.70-8.99 (m, 3H, pyridyl)[e]
2i	102-104	1635, 1580, 1545, 1370, 1305, 1135^c	2.43 (s, 3H, Me); 3.17 (s, 3H, Me); 7.50 (s, 1H, CH); 7.53-7.80 and 8.33-8.57 and 8.73-8.93 (m, 3H, pyridyl)[e]
2j	108-110	1620, 1595, 1525, 1345, 1325, 1150^c	2.45 (s, 6H, 2 Me); 7.20-8.03 (m, 6H, CH and Ar and pyridyl); 8.23-8.50 and 8.67-8.83 (m, 2H, pyridyl)[e]
2k	154-156	3330, 1650, 1597, 760^c	2.52 (s, 3H, Me); 7.10-8.26 (m, 9H, CH and Ar); 10.55 (br. s, 1H, NH, D_2O exchange)[f]
2l	152-154	3350, 1670, 1590, 1245, 825^c	2.47 (s, 3H, Me); 3.77 (s, 3H, OMe); 6.73-8.40 (m, 9H, CH and Ar); 10.58 (br. s, 1H, NH, D_2O exchange)[f]

a) Mps are uncorrected and frequently occur with decomposition. b) Neat. c) Nujol mull. d) Mixture of isomers. e) In chloroform-d using TMS as internal standard. f) In dimethylsulfoxide-d_6 using TMS as internal standard.

ethyl acetate (1a-h, 1k and 1l) or 50 ml of methylene chloride (1i and 1j), and saturated aqueous sodium carbonate (3x30 ml). Within a few minutes (see Table 1), the dehydrohalogenation of the bromo derivative into related azoalkene 2 was complete, with the exception of azoalkene 2b for which the complete formation required base for 24 hrs with magnetic

Table 3. Elemental Analyses of Azoalkenes (**2**)

Product (2)	Formula	Calculated (Found)
2a	$C_{14}H_{19}N_3O$	C, 68.54; H, 7.80; N, 17.12 (C, 68.32; H, 7.92; N, 17.09)
2b	$C_{21}H_{17}N_3O$	C, 77.04; H, 5.23; N, 12.83 (C, 77.21; H, 5.02; N, 12.98)
2c	$C_{11}H_{15}N_2O_3P$	C, 51.97; H, 5.94; N, 11.01 (C, 52.09; H, 5.97; N, 11.18)
2d	$C_{16}H_{16}N_2O_2S$	C, 63.97; H, 5.37; N, 9.32 (C, 63.77; H, 5.29; N, 9.41)
2e	$C_{20}H_{15}N_5O_3$	C, 64.33; H, 4.05; N, 18.76 (C, 64.21; H, 3.91; N, 18.84)
2f	$C_{15}H_{12}ClN_5O_3$	C, 52.11; H, 3.50; N, 20.25 (C, 52.31; H, 3.44; N, 20.18)
2g	$C_{16}H_{15}N_5O_4$	C, 56.30; H, 4.43; N, 20.52 (C, 56.19; H, 4.38; N, 20.71)
2h	$C_{10}H_{13}N_4O_5P$	C, 40.00; H, 4.36; N, 18.66 (C, 40,29; H, 4.19, N, 18.57)
2i	$C_9H_{10}N_4O_4S$	C, 39.99; H, 3.73; N, 20.73 (C, 39.81; H, 3.85; N, 20.71)
2j	$C_{15}H_{14}N_4O_2S$	C, 57.30; H, 4.48; N, 17.82 (C, 57.49; H, 4.31; N, 17.68)
2k	$C_{17}H_{13}ClN_4OS$	C, 57.22; H, 3.67; N, 15.70 (C, 57.09; H, 3.55; N, 15.84)
2l	$C_{18}H_{16}N_4O_2S$	C, 61.34; H, 4.57; N, 15.89 (C, 61.23; H, 4.47; N, 16.02)

stirring. The red organic phase was washed with water (3x30 ml), separated, dried over anhydrous sodium sulfate and evaporated under reduced pressure with gentle heating. Except for 2a and 2c which are oils and purified by chromatography on a silica gel column (elution with methylene chloride or cyclohexane-ethyl acetate mixtures), the remaining products 2 were normally purified by crystallization from ethyl acetate (10 ml)/n-pentane (5 ml) or petroleum ether bp 40-60° (5 ml). In a few cases (2g, 2h and 2j) a preliminary purification of the reaction mixture on a silica gel column in the same conditions as above was necessary. All the products are red.

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SYNTHESIS OF N-PYRROLYL ACIDS

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A series of N-pyrrolyl acids have been synthesized in order to study their pharmacological properties.[1] Yur'ev[2] described a method for the