A Useful Synthesis of 3-Halogeno-1-azabutadiene Derivatives, and Their Applicability in the Preparation of Heterocycles

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Azabutadiene derivatives (1) are halogenated in a selective manner with *N*-chlorosuccinimide or *N*-bromosuccinimide at the C_β-enamine carbon. The resultant halogenated compounds (3) are suitable precursors for the synthesis of 2-oxopyrimidines and 1,2,6-thiadiazine *S*-oxides containing a halogen at C-5 and C-4 respectively, and also for substituted 4-chloro- and 4-bromo-pyrazoles.

In previous papers we have reported the versatility of 1-azabutadiene derivatives (1) in the synthesis of five- and six-membered nitrogen-containing heterocycles.[1] The reaction of these compounds (1) with sulphur dichloride or thionyl chloride leads to different thiadiazines. By contrast, the reaction of (1) with sulphuryl chloride affords dihalogenated di-imines [2] instead of the corresponding thiadiazine; however, halogenated compounds are obtained in low yield in this reaction. For this reason, other halogenating reagents have been surveyed for their ability to functionalize the azabutadienes (1).

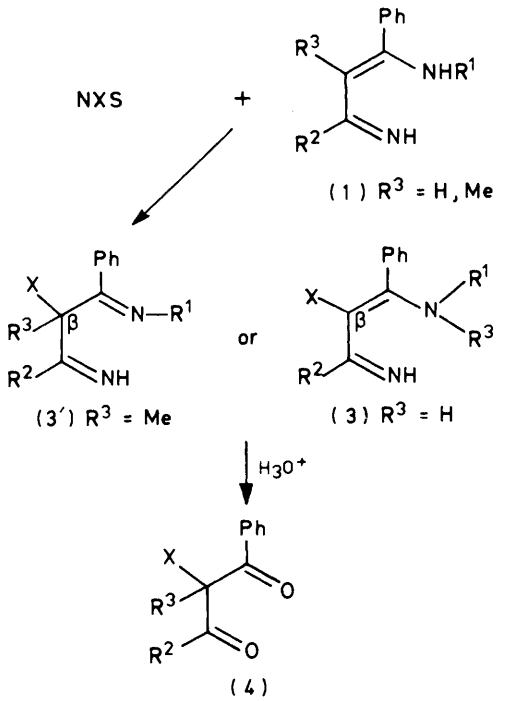
N-Chlorosuccinimide (NCS) and *N*-bromosuccinimide (NBS) have been widely used in the halogenation of enaminic [3] and iminic [4] compounds and for the introduction of halogen into heterocyclic rings;[5] we have therefore studied the behaviour of NXS (X = Cl, Br) towards azabutadienes (1) and investigated the synthetic utility of the products.

Results and Discussion

Halogenation of 1-Azabutadienes Derivatives.—1-Azabutadiene derivatives (1) react with *N*-chloro- and *N*-bromosuccinimide (NXS) (2) at room temperature in toluene to afford monohalogenated di-imines (3) and (3′) in high yields (Table 1). The halogenation is regiospecific and occurs at the C_β-enamine carbon when stoicheiometric amounts of (1) and (2) are used. The structure of compounds (3) and (3′) depends on the substitution pattern in the starting azabutadiene. From (1; R^3 = H), derived from acetophenone, compounds (3) are isolated as 1,3-dienes; the off-resonance ^{13}C n.m.r. spectra of these shows one singlet centred at *ca.* 90 p.p.m., which is attributed to the sp^2 hybridized carbon linked to halogen.

The halogenated azabutadienes (3) with their conjugated diene structure are potentially useful for the synthesis of heterocycles by double condensation processes, and are probably more suitable than the di-imines (3′).† We investigated this possibility.

Heating of compounds (3) and (3′) at 60 °C in concentrated hydrochloric acid afforded the corresponding dicarbonyl compounds (4). It was found that in protic media, the halogenated di-imines (3) are more stable than the parent 1-azabutadienes (1) ‡ (Scheme 1). However, the dicarbonyl compounds (4) can also be obtained by treatment of the corresponding 1,3-diketone with *N*-halogenosuccinimide.



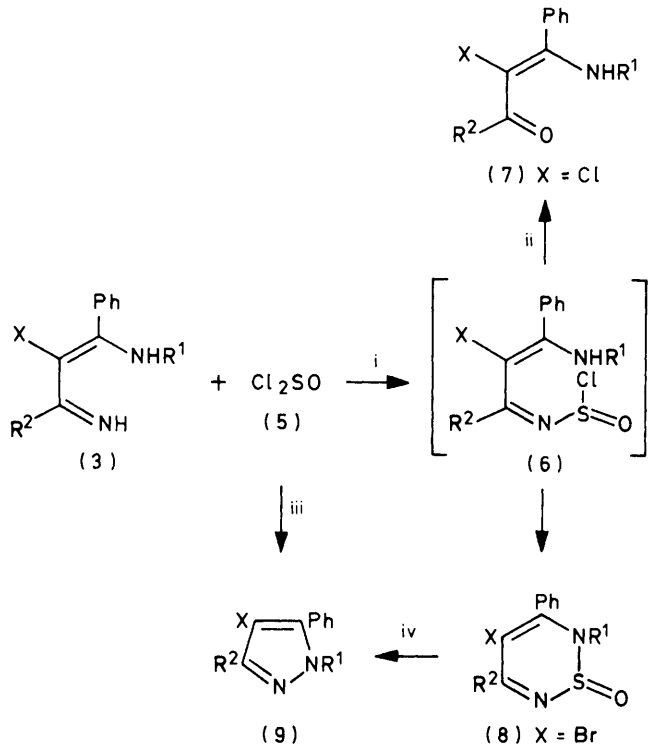
Scheme 1.

Synthesis of Halogen-containing Heterocycles.—We have started a systematic study on the reactivity of halogenated 1-azabutadienes (3) with different substrates which can give double condensation reactions. We first selected the reaction with thionyl chloride and ethyl chloroformate, since these compounds react with 1-azabutadienes (1) under very mild conditions to afford thiadiazines [6] and pyrimidinones [7] in a regioselective fashion.

We studied the reaction of (3) with thionyl chloride giving 1,2,6-thiadiazine *S*-oxides (8). However, more vigorous reaction conditions are required than when the parent azabutadienes (1) were used in a similar process.[6] Thionyl chloride does not react with (3; X = Cl) at room temperature in pyridine. When the temperature is raised to 70 °C, the enaminoketones (7) are isolated instead of the thiadiazines (8). The formation of compounds (7) is rationalized by hydrolysis of the corresponding intermediate (6). This reaction shows the enhanced reactivity of the unsubstituted NH in the azabutadiene [1] (Scheme 2).

The 4-chloropyrazoles (8) are produced when the reaction of the azabutadienes (3) and thionyl chloride is carried out at 100 °C. The heterocycles (9) derive from compounds (8) by N–N bond formation with SO extrusion.

† The same dihalogenated compounds are obtained on treatment of (1) with 2 mol of either NCS or sulphuryl chloride. The study of the behaviour of these halogenodi-imines is now in progress.
‡ Treatment of (1) with 3M-H_2SO_4 yields the corresponding dicarbonyl compounds. However, in these reaction conditions, the hydrolysis of the products (3) does not take place.



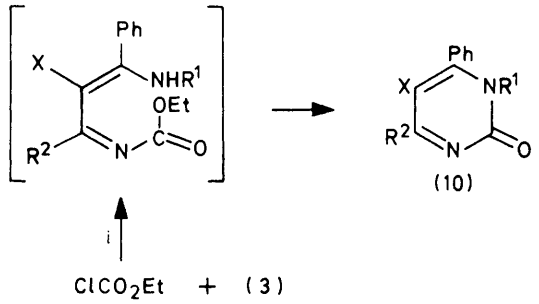
Scheme 2. *Reagents:* i, pyridine, 25 °C; ii, H_2O; iii, pyridine, 100 °C; iv, toluene, 100 °C

The 1,2,6-thiadiazines (8) could be isolated from the brominated 1-azabutadienes (3; X = Br). In this case, the reaction of (3) and thionyl chloride takes place at room temperature in *ca.* 20 h. The pyrazoles (9) are isolated when the heterocycles (8; X = Br) are heated at 100 °C in toluene solution. Compounds (9) can also be obtained *in situ* when (1) reacts with thionyl chloride in pyridine at 100 °C.

Compounds (1) and ethyl chloroformate yield pyrimidin-2-(1*H*)-ones in a regioselective manner.[7] For this reason, we also studied the behaviour of compounds (3) towards ethyl chloroformate as a route to the halogenated pyrimidinones (10). The halogenated 1-azabutadienes (3) also show in this case a diminished reactivity compared with the parent 1-azabutadienes (1), especially when X = Cl.

Temperatures of 100 °C were used in the synthesis of 5-bromo-2-oxopyrimidines by reaction of compounds (3) with ethyl chloroformate in pyridine solution. However, organometallics (methyl-lithium) had to be used to promote the reaction which leads to the formation of the 5-chloro-2-oxopyrimidines (10) (Scheme 3).

The results obtained in this type of heterocyclization suggest that 1-azabutadienes (1) are more reactive than their halogenated homologues (3). The reactivity of these 1-azabutadienes is modified by electronic factors.



Scheme 3. *Reagents:* i, MeLi (when X = Cl) or pyridine, 100 °C (when X = Br)

Experimental

M.p.s were taken on samples in open capillary tubes in a Buchi melting point apparatus and are uncorrected. The n.m.r. spectra were obtained using a Varian FT-80 n.m.r. spectrometer using deuteriated chloroform as solvent and shifts are reported in δ(p.p.m.) downfield from internal tetramethylsilane. I.r. spectra were recorded on a Pye Unicam instrument. Mass spectra were taken on a Hewlett Packard 5930 A spectrometer. Microanalyses were performed on a Perkin-Elmer Model 240. Ether refers to diethyl ether. Full i.r. and ^{1}H n.m.r. data for compounds (3), (3′), (4), (8), (9), and (10) are given as a Supplementary Publication * (SUP No. 23698, 3 pages).

Halogenodi-imines (3) *and* (3′). *General Procedure.* 2-*Chloro*-3-*imino*-1,3-*diphenyl*-N-(p-*tolyl*)*prop*-1-*enamine* (3c).—*N*-Chlorosuccinimide (1.35 g, 10 mmol) was added to a solution of 3-imino-1,3-diphenyl-*N*-(*p*-tolyl)prop-1-enamine (3.12 g, 10 mmol) in toluene (80 ml) at room temperature. After being stirred for 3 h, the mixture was poured into 3M-KOH (150 ml) and extracted with ether. The organic layer was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by recrystallization from hot hexane to afford the *enamine* (3c) (2.8 g, 80%); $\nu_{max.}$ (Nujol) 3 400 and 1 600 cm^{-1}; δ($CDCl_3$) 2,3 (3 H, s, Me), 4.1 (1 H, br, NH), and 6.3—7.8 (14 H, m, arom.); δ(^{13}C) ($CDCl_3$) 161.9 (s), 148.0(s), 144.2(s) 139.1(s), 135.6(s), 132.6(s), 130.2(d), 128.9(d), 128.6(d), 128.0(d), 127.6(d), 126.1(d), 122.0(d), 120.7(d), 96.1(s), and 20.7 p.p.m. (q). Physical and analytical properties of compounds (3) and (3′) are given in Table 1.

2-*Bromo*-1-*phenyl*-3-(p-*tolyl*)*propane*-1,3-*dione* (4d).—A solution of 2-bromo-3-imino-1-phenyl-*N*,3-di-*p*-tolylprop-1-enamine (3h) (4.0 g, 10 mmol) and concentrated HCl (50 ml) in THF was stirred at 70 °C for 6 h, then poured into ice-cooled water and extracted with ether. The dry organic layer was evaporated and the residue was purified by recrystallization from hot hexane to afford the *dione* (4h) (2.6 g, 82%); $\nu_{max.}$ (Nujol) 1670 and 1 630 cm^{-1}; δ($CDCl_3$) 2.4 (3 H, s, Me), 6.5 (1 H, s, BrCH), and 7.1—8.1 (9 H, m, arom.); δ (^{13}C) ($CDCl_3$) 188.6(s), 188.2(s), 145.0(s), 133.7(s), 130.8(s), 129.3(d), 128.9(d), 128.7(d), 128.5(d), 128.1(d), 52.5(d), and 21.2 p.p.m. (q).

Physical and analytical properties of compounds (4) are given in Table 1.

2-*Chloro*-1,3-*diphenyl*-3-(p-*tolylamino*)*prop*-2-*en*-1-*one* (7; R^1 = *p*-tolyl, R^2 = Ph).—Thionyl chloride (1.8 g, 14 mmol) was added to a solution of 2-chloro-3-imino-1,3-diphenyl-*N*-*p*-tolylprop-1-enamine (3c) (3.5 g, 10 mmol) in pyridine (70 ml) at 0 °C and the mixture was allowed to warm to 70 °C. After being stirred for 7 h the solution was poured into ice-cooled 2M-H_2SO_4 (200 ml). The resulting mixture was extracted with ether, and the organic layer dried (Na_2SO_4), filtered, and evaporated. The residue was purified by recrystallization from hot hexane to afford the *enone* (7; R^1 = *p*-tolyl, R^2 =

* For details of the Supplementary Publications Scheme see Instructions to Authors (1983) in *J. Chem. Soc., Perkin Trans. 1*, 1983, Issue 1.

Table 1. Properties of the halogenodi-imines (3) and (3′) and their dicarbonyl analogues (4), obtained from the di-imines (1) and NXS (2)

Product	R^1	R^2	R^3	X	Yield (%)	M.p. (°C)	Found (%) (Required) C	H	N
(3a)	Ph	Ph	H	Cl	82	147—148	76.0 (75.78)	5.0 (5.15)	8.1 (8.42)
(3b)	Ph	*p*-Tolyl	H	Cl	83	112—113	76.3 (76.18)	5.7 (5.52)	7.8 (8.08)
(3c)	*p*-Tolyl	Ph	H	Cl	80	129—130	76.4 (76.18)	5.2 (5.52)	7.9 (8.08)
(3d)	*p*-Tolyl	*p*-Tolyl	H	Cl	83	144—145	76.7 (76.55)	5.4 (5.86)	7.4 (7.76)
(3e)	*p*-Tolyl	Cyclohexyl	H	Cl	79	139—140	74.5 (74.88)	7.4 (7.14)	7.6 (7.94)
(3f)	Ph	Ph	H	Br	80	99—100	67.1 (66.85)	4.3 (4.54)	7.2 (7.42)
(3g)	*p*-Tolyl	Ph	H	Br	81	116—117	67.8 (67.52)	4.5 (4.89)	7.0 (7.16)
(3h)	*p*-Tolyl	*p*-Tolyl	H	Br	82	155—156	67.9 (68.15)	5.3 (5.22)	6.7 (6.91)
(3′i)	Ph	Ph	Me	Cl	74	Oil	76.3 (76.18)	5.2 (5.52)	7.9 (8.08)
(3′j)	Ph	*p*-Tolyl	Me	Cl	72	Oil	76.9 (76.55)	6.2 (5.86)	8.2 (7.76)
(3′k)	Ph	*p*-Tolyl	Me	Br	75	Oil	67.9 (68.15)	5.4 (5.22)	6.5 (6.91)
(4a)		Ph	H	Cl	85	83—85	69.3 (69.64)	4.2 (4.28)	
(4b)		*p*-Tolyl	H	Cl	87	104—106	70.8 (70.46)	4.4 (4.80)	
(4c)		Cyclohexyl	H	Cl	80	Oil	67.9 (68.05)	6.1 (6.47)	
(4d)		*p*-Tolyl	H	Br	82	109—111	60.3 (60.58)	4.0 (4.13)	
(4e)		Ph	Me	Cl	78	129—131	70.8 (70.46)	4.6 (4.80)	

Ph) (2.5 g, 72%), m.p. 139—141 °C (Found: C, 76.1; H, 5.0; N, 3.9. $C_{22}H_{18}ClNO$ requires C, 75.96; H, 5.22; N, 4.02%); $\nu_{max.}$ (Nujol) 1 600 and 1 560 cm^{-1}; δ($CDCl_3$) 2.2 (3 H, s, Me), 6.5—7.7 (14 H, m, arom.), and 9.8 (1 H, br, NH); δ(^{13}C) ($CDCl_3$) 192.6(s), 160.0(s), 140.6(s), 136.4(s), 134.2(s) 133.6(s), 130.4(s), 129.9(d), 129.2(d), 128.8(d), 128.2(d), 127.9(d), 123.2(d), 102.4(s), and 20.4 p.p.m. (q); *m/z* 347 (M^+).

4-*Bromo*-3,5-*diphenyl*-2-(p-*tolyl*)-1,2,6-*thiadiazine* S-*Oxide* (8b).—Thionyl chloride (1.8 g, 14 mmol) was added to a solution of 2-bromo-3-imino-1,3-diphenyl-*N*-*p*-tolylprop-1-enamine (3g) (3.9 g, 10 mmol) in pyridine (80 ml) at 0 °C and the mixture was allowed to warm to room temperature. After being stirred for 24 h the solution was poured into ice-cooled 2M-H_2SO_4 (200 ml). The resulting mixture was extracted with ether, and the organic layer dried (Na_2SO_4), filtered, and evaporated. The residue was recrystallised from hexane–chloroform to give the *thiadiazine* (8b) (3.4 g, 78%); $\nu_{max.}$ (Nujol) 1 130 cm^{-1}; δ($CDCl_3$) 2.2 (3 H, s, Me), 6.7—8.0 (14 H, m, arom.); δ(^{13}C) ($CDCl_3$) 163.7(s), 148.5(s), 138.0(s), 137.7(s), 136.5(s), 133.8(d), 130.6(d), 129.9(d), 129.5(d), 128.7(d), 128.0(d), 127.7(d), 126.3(d), 98.2(s), and 20.7 p.p.m. (q); *m/z* 436 (M^+).

4-*Chloro*-5-*phenyl*-1,3-*di*-p-*tolylpyrazole* (9b).—A mixture of 2-chloro-3-imino-1-phenyl-N,3-di-*p*-tolylprop-1-enamine (3d) (3.6 g, 10 mmol) and thionyl chloride (1.8 g, 14 mmol) in pyridine (70 ml) was heated at 100 °C for 8 h, and then slowly poured into ice-cooled 2M-H_2SO_4 (200 ml). The resulting mixture was extracted with ether and the organic layer dried (Na_2SO_4), filtered, and evaporated. The residue was purified by recrystallization from hot hexane–THF to afford the *pyrazole* (9b) (2.7 g, 75%); $\nu_{max.}$ (Nujol) 1 640 cm^{-1}; δ($CDCl_3$) 2.3 (3 H, s, Me), 2.4 (3 H, s, Me), and 7.0—8.0 (13 H, m, arom.); δ(^{13}C) ($CDCl_3$) 148.6(s), 142.0(s), 138.0(s), 137.7(s), 137.2(s), 130.0, 129.3, 128.7, 128.3, 128.0, 127.5, 124.6, 108.2(s), 21.1(q), and 20.8 p.p.m. (q); *m/z* 358 (M^+).

4-*Bromo*-5-*phenyl*-1,3-*di*-p-*tolylpyrazole* (9e).—A solution of 4-bromo-3-phenyl-2,5-di-(*p*-olyl-1,2,6-thiadiazine *S*-oxide (8c) (2.3 g, 5 mmol) in toluene (60 ml) was heated at 100 °C for 8 h; evaporation of the solvent under reduced pressure then gave the heterocycle (9e). This *compound* (1.7 g, 84%) was purified by rectystallization from hot hexane–THF; $\nu_{max.}$ (Nujol) 1 620 cm^{-1}; δ($CDCl_3$) 2.2 (3 H, s, Me), 2.3 (3 H, s, Me), 6.7—8.0 (13 H, m, arom.); δ(^{13}C) ($CDCl_3$) 149.3(s), 141.7(s), 137.8(s), 137.4(s), 137.2(s), 130.1(s), 129.8(d), 129.3(d), 128.9(d), 128.7(d), 128.3(d), 127.8(d), 124.5(d), 94.4(s), 21.2(q), and 20.9 p.p.m. (q); *m/z* 403 (M^+).

5-*Chloro*-1,2-*dihydro*-2-*oxo*-1,4,6-*triphenylpyrimidine* (10a).—Methyl-lithium (20 mmol) was added under argon to a solution of 2-chloro-3-imino-*N*,1,3-triphenylprop-1-enamine (3a) (3.3 g, 10 mmol) in anhydrous THF (50 ml). After 30 min, ethyl chloroformate (1.1 g, 10 mmol) was added. After being stirred for 4 h at room temperature, the mixture was poured into ice-cooled water and extracted with ether. The dry organic layer was evaporated and the residue recrystallized from hexane–chloroform to afford the *pyrimidine* (10a) (2.2 g, 62%): $\nu_{max.}$ (Nujol) 1 670 cm^{-1}; δ($CDCl_3$) 6.8—8.0 (15 H, m, arom.).

5-*Bromo*-1,2-*dihydro*-2-*oxo*-4,6-*diphenyl*-1-p-*tolylpyrimidine* (10e).—A solution of 2-bromo-3-imino-1,3-diphenyl-*N*-*p*-

Table 2. Properties of the heterocycles (8), (9), and (10) obtained from the halogenodi-imines (3)

Product	R^1	R^2	X	Yield (%)	M.p. (°C)	Found (%) (Required) C	H	N
(8a)	Ph	Ph	Br	82	165—167	56.7 (56.83)	5.5 (5.75)	5.8 (5.97)
(8b)	*p*-Tolyl	Ph	Br	78	141—142	60.2 (60.42)	3.6 (3.97)	6.3 (6.40)
(8c)	*p*-Tolyl	*p*-Tolyl	Br	74	168—170	61.6 (61.34)	4.1 (4.25)	6.0 (6.22)
(8d)	*p*-Tolyl	Cyclohexyl	Br	72	122—123	60.2 (59.60)	5.4 (5.23)	6.2 (6.32)
(9a)	*p*-Tolyl	Ph	Cl	78	106—107	76.8 (76.63)	5.3 (4.97)	7.9 (8.12)
(9b)	*p*-Tolyl	*p*-Tolyl	Cl	75	152—154	76.3 (76.96)	5.1 (5.34)	7.5 (7.81)
(9c)	*p*-Tolyl	Cyclohexyl	Cl	73	118—119	75.5 (75.31)	6.3 (6.61)	7.6 (7.98)
(9d)	*p*-Tolyl	Ph	Br	80	116—118	67.5 (67.88)	4.3 (4.40)	7.0 (7.19)
(9e)	*p*-Tolyl	*p*-Tolyl	Br	84	134—135	68.8 (68.49)	4.4 (4.75)	6.5 (6.94)
(9f)	*p*-Tolyl	Cyclohexyl	Br	80	107—109	67.5 (67.18)	5.5 (5.89)	6.9 (7.12)
(10a)	Ph	Ph	Cl	62	228—230	73.3 (73.64)	3.9 (4.21)	7.5 (7.81)
(10b)	*p*-Tolyl	Ph	Cl	65	237—239	73.9 (74.09)	4.7 (4.59)	7.4 (7.51)
(10c)	*p*-Tolyl	Cyclohexyl	Cl	64	223—225	73.3 (72.91)	5.9 (6.12)	7.1 (7.39)
(10d)	Ph	Ph	Br	70	237—239	65.9 (65.52)	3.5 (3.75)	6.5 (6.95)
(10e)	*p*-Tolyl	Ph	Br	70	249—250	66.5 (66.20)	4.3 (4.10)	6.5 (6.71)

tolylprop-1-enamine (3g) (3.9 g, 10 mmol) and ethyl chloroformate (1.1 g, 10 mmol) in pyridine (100 ml) was heated at 100 °C for 6 h, and then slowly poured into ice-cooled 2M-H_2SO_4 (200 ml). The resulting solution was extracted with ether, dried, and evaporated to give the *pyrimidine* (10e) (2.9 g, 70%), recrystallized from hexane–chloroform; $\nu_{max.}$ (Nujol) 1 670 cm^{-1}; $\delta(CDCl_3)$ 2.2 (3 H, s, Me) and 6.7—8.1 (14 H, m, arom.).

Physical and analytical properties of compounds (8)—(10) are given in Table 2.

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