Site-Selective and Regioselective Cycloaddition of *N*-Propadienylanilines with Nitrile Oxides. Claisen-Type Rearrangement of the Cycloadducts

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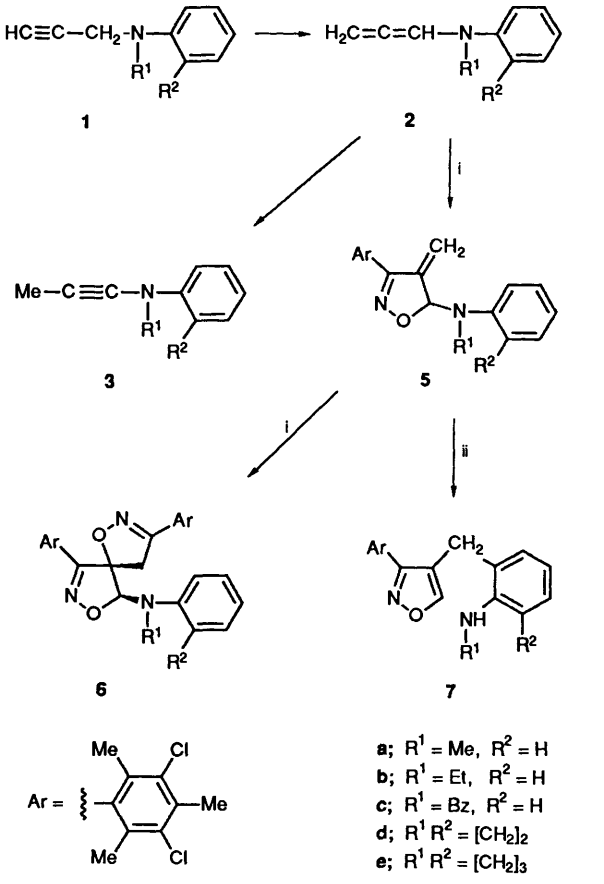
The reaction of *N*-propadienylanilines with 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide proceeds in a site-selective and regioselective fashion to give 5-substituted 4-methylene-4,5-dihydroisoxazoles. The latter compounds (*i*) add a second molecule of nitrile oxide to afford 4,5′-spirobi-(4,5-dihydroisoxazoles) and (*ii*) isomerise to 4-(2-aminobenzyl)isoxazoles through a Claisen-type rearrangement.

1,3-Dipolar cycloadditions to allenes are worthy of investigation as the resulting adducts still contain an ethylenic bond which can facilitate further transformations of synthetic utility.[1,2] However, allenes present two positions as well as two orientations for attack. Hence, for synthetic purposes, it is desirable to have a type of substitution capable of exerting site- and regiocontrolling effects. In this context, we focused our attention on the behaviour of *N*-propadienylanilines towards 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide.

Results and Discussion

The allenic substrates **2a–e** were synthesized upon isomerisation of the alkyne derivatives **1a–e** in the presence of potassium t-butoxide (see Scheme 1). The reaction conditions, which are reported in Table 1, had to be carefully chosen in order to minimise the further isomerisation of the first formed aminoallenes to the corresponding ynamines **3a–e**. Nevertheless, the latter species were usually present as impurities in the desired allenes.

The reaction between nitrile oxide **4** and compounds **2a–e** were carried out in boiling tetrachloromethane by using both 1:1 and 2:1 molar ratios of the reactants. Times, products and yields are collected in Table 2. The monoadduct structures **5a–e** were readily assigned on the basis of their ^{1}H NMR spectra (Table 3), which exhibited the typical set of signals of 5-monosubstituted 4-methylene-4,5-dihydroisoxazoles.[3–5] We then ascertained that compounds **5a–e** reacted further with nitrile oxide **4** to afford the diadducts **6a–e** in high yield. The 4,5′-junction in the latter spiro-compounds was unequivocally established by both ^{1}H and ^{13}C chemical shifts as well as by the coupling constant of the isoxazolinic protons.[4–9] However, the relative configuration of the two stereocentres of spiro products



Scheme 1 *Reagents:* i, ArCNO **4**; ii, $ZnCl_2$.

Table 1 Preparation of aminoallenes **2a–e**[a]

Allene	Bu^{t}OK (mol equiv.)[b]	Temp. (T/°C)	Time (t/min)	Yield (%)	Purity[c,d] (%)	$\delta_H(CDCl_3)$
2a	0.14	20	3	71	85	3.08 (3 H, s), 5.45 (2 H, d, *J* 6), 6.7–7.4 (6 H, overlapping)
2b	0.34	40	5	64	85	1.18 (3 H, t, *J* 7), 3.58 (2 H, q, *J* 7), 5.42 (2 H, d, *J* 6), 6.6–7.3 (6 H, overlapping)
2c	0.34	25	3	75	88	4.72 (2 H, s), 5.32 (2 H, d, *J* 6), 6.7–7.4 (11 H, overlapping)
2d[e]	0.34	31	5	90	95	3.08 (2 H, t, *J* 8), 3.58 (2 H, t, *J* 8), 5.48 (2 H, d, *J* 6), 6.5–7.2 (5 H, overlapping)
2e	0.68	28	5	83	86	1.7–2.1 (2 H, m), 2.76 (2 H, t, *J* 6), 3.34 (2 H, t, *J* 6), 5.45 (2 H, d, *J* 6), 6.5–7.2 (5 H, overlapping)

[a] All compounds listed were obtained as undistillable oils; samples of analytical purity were not available. [b] In THF. [c] By NMR analysis. [d] Ynamines **3a–e** were the major impurities. [e] $\delta_C(CDCl_3)$ 27.9 (t), 49.5 (t), 87.0 (t), 101.3 (d), 106.5 (d), 118.5 (d), 125.0 (d), 127.7 (d), 129.9 (s), 147.5 (s) and 203.7 (s).

6a–e was assumed to be (4*R**,5*R**) upon analogy with that determined by X-ray analysis of a similar 4,5′-spirobi-(4,5-dihydroisoxazole).[5]

Table 2 Reaction of aminoallenes **2a–e** with nitrile oxide **4**[a]

Allene	4 (mol. equiv.)	Time (*t*/h)	Products (% yields)[b] **5**	**6**	Eluent[c]
2a	1	8	35	20	LP–toluene (1:1)
	2	16		77	LP–toluene (1:1)
2b	1	10	66	3	Dichloromethane
	2	15	21	53	Toluene
2c	1	18	54	11	LP–ethyl acetate (20:1)
	2	20	22	44	Toluene
2d	1	5	55	8	LP–ethyl acetate (15:1)
	2	20	17	43	Toluene
2e	1	14	75	6	LP–ethyl acetate (10:1)
	2	16	40	27	LP–ethyl acetate (20:1)

[a] In boiling tetrachloromethane. [b] Yields refer to the starting moles of the allene. [c] LP = light petroleum.

The subsequent stage of our investigation was carried out with the idea that compounds **5a–e** might be susceptible to a Claisen-type rearrangement of the *N*-allylaniline portion. Upon heating, they were slowly converted into the isomeric 4-(2-aminobenzyl)isoxazoles **7a–e**. The formation of the latter products was greatly accelerated in the presence of anhydrous zinc chloride (Table 4). Only compound **5d** showed some reluctance to undergoing this rearrangement, probably owing to geometric restraints operating against the intramolecular approach necessary for the [3,3]-sigmatropic process.

The results presented here constitute clear evidence that allenic substrates of type **2** are fruitful dipolarophiles because the amino substituent acts as an efficient site- and regio-directing tool. This outcome is peculiar to aminoallenes, since a wider product distribution, due to a poorer degree of selectivity, has been found in the reaction of nitrile oxides with monosubstituted allenes carrying other groups such as methoxy,[6] phenoxy,[6,10] phenylthio,[11] phenylsulphonyl,[12,13] *N*-heteroaryl[5] and methoxycarbonyl.[6] The dipolarophilic behaviour of compounds **2** can be related to their enamine-like structure; in other words the strongly electron-donating substituent activates the α,β-double bond and at the same time concentrates the HOMO at the β-

Table 3 Characterisation of 4,5-dihydroisoxazole derivatives **5a–e** and **6a–e**

Compd.	M.p. (°C)[a]	M^+ (*m*/*z*)	$\delta_H(CDCl_3)$	$\delta_C(CDCl_3)$	Found (%) (Required) C	H	N
5a	153–154 (PhH–hexane)	374	2.29 (6 H, s), 2.60 (3 H, s), 2.97 (3 H, s), 5.21 (1 H, d, *J* 3), 5.45 (1 H, d, *J* 3), 6.68 (1 H, t, *J* 3), 6.9–7.4 (5 H, m)		64.1 (64.0)	5.6 (5.4)	7.5 (7.5)
5b	104–105 (PhH–hexane)	388	1.18 (3 H, t, *J* 7), 2.13 (3 H, s), 2.29 (3 H, s), 2.60 (3 H, s), 3.49 (2 H, q, *J* 7), 5.14 (1 H, d, *J* 3), 5.41 (1 H, d, *J* 3), 6.52 (1 H, t, *J* 3), 7.0–7.4 (5 H, m)		64.7 (64.8)	5.6 (5.7)	7.3 (7.2)
5c	108–109 (hexane)	450	2.01 (3 H, s), 2.27 (3 H, s), 2.58 (3 H, s), 4.61 (2 H, s), 5.05 (1 H, d, *J* 3), 5.42 (1 H, d, *J* 3), 6.68 (1 H, t, *J* 3), 6.9–7.4 (10 H, m)		69.2 (69.2)	5.3 (5.4)	6.0 (6.2)
5d	190–191 (PhH–hexane)	386	2.27 (6 H, s), 2.58 (3 H, s), 3.02–3.08 (2 H, m), 3.36–3.57 (2 H, m), 5.23 (1 H, d, *J* 3), 5.55 (1 H, d, *J* 3), 6.79–6.86 (3 H, overlapping), 7.12–7.17 (2 H, m)		65.2 (65.1)	5.2 (5.2)	7.1 (7.2)
5e	172–173 (PhH–hexane)	400	1.89–2.06 (2 H, m), 2.28 (3 H, s), 2.31 (3 H, s), 2.57 (3 H, s), 2.68–2.90 (2 H, m), 3.12–3.43 (2 H, m), 5.21 (1 H, d, *J* 3), 5.41 (1 H, d, *J* 3), 6.82 (1 H, t, *J* 8), 6.93 (1 H, t, *J* 3), 7.05 (2 H, m), 7.14 (1 H, t, *J* 8)		65.7 (65.8)	5.6 (5.5)	7.0 (7.0)
6a	206–208 (PhH–$CHCl_3$)	603	1.82 (6 H, s), 2.33 (3 H, s), 2.46 (3 H, s), 2.60 (3 H, s), 2.62 (3 H, s), 2.90 (3 H, s), 2.95 and 3.43 (2 H, AB, *J* 18), 6.35 (1 H, s), 6.8–7.4 (5 H, m)	17.0 (q), 19.0 (q), 19.1 (q), 19.8 (q), 20.0 (q), 32.8 (q), 41.3 (t), 99.6 (s), 100.1 (d), 116.9 (d), 121.5 (d), 126.1–136.9, 148.5 (s), 156.4 (s)	59.6) (59.5)	4.7 (4.8)	6.7 (6.9)
6b	180–181 (PhH–hexane)	617	1.23 (3 H, t, *J* 7), 1.73 (6 H, s), 2.20 (3 H, s), 2.50 (3 H, s), 2.58 (3 H, s), 2.60 (3 H, s), 2.82, 3.43 (2 H, AB, *J* 18), 3.08–3.55 (2 H, m), 6.25 (1 H, s), 6.9–7.4 (5 H, m)	14.2 (q), 16.9 (q), 18.7 (q), 18.9 (q), 19.3 (q), 19.9 (q), 41.3 (t), 43.2 (t), 99.3 (s), 101.5 (d), 120.2 (d), 122.2 (d), 126.1–136.7, 146.0 (s), 156.16 (s), 156.24 (s)	60.0 (60.1)	5.1 (5.0)	6.9 (6.8)
6c	191–192 (PhH–hexane)	679	1.61 (6 H, s), 2.10 (3 H, s), 2.50 (3 H, s), 2.59 (6 H, s), 2.81, 3.53 (2 H, AB, *J* 18), 4.32, 4.65 (2 H, AB, *J* 15), 6.47 (1 H, s), 6.9–7.3 (10 H, m)	17.0 (q), 19.0 (q), 19.5 (q), 20.0 (q), 41.5 (t), 46.2 (t), 99.7 (s), 100.2 (d), 119.9 (d), 122.6 (d), 126.0–137.5, 146.2 (s), 156.4 (s), 156.7 (s)	63.4 (63.4)	4.8 (4.9)	6.2 (6.2)
6d	265–267 (PhH)	615	1.75 (6 H, s), 2.31 (3 H, s), 2.46 (3 H, s), 2.54 (3 H, s), 2.58 (3 H, s), 2.96, 3.61 (2 H, AB, *J* 18), 3.02–3.25 (3 H, m), 3.53–3.62 (1 H, m), 6.39 (1 H, s), 6.85 (2 H, m), 7.18 (2 H, m)	17.2 (q), 18.8–20.1, 28.6 (t), 41.1 (t), 45.9 (t), 95.7 (d), 99.0 (s), 108.5 (d), 120.8 (d), 125.1 (d), 125.3–137.0, 149.2 (s), 155.6 (s), 156.6 (s)	60.5 (60.3)	4.7 (4.7)	6.7 (6.8)
6e	255–256 (PhH–hexane)	629	1.66 (6 H, s), 1.8–2.2 (2 H, m), 2.31 (3 H, s), 2.34 (3 H, s), 2.56 (3 H, s), 2.58 (3 H, s), 2.7–3.1 (3 H, m), 2.89, 3.31 (2 H, AB, *J* 18), 3.4–3.6 (1 H, m), 6.46 (1 H, s), 6.6–6.9 (2 H, m), 7.0–7.2 (2 H, m)	17.0 (q), 18.9 (q), 19.0 (q), 19.8 (q), 20.0 (q), 22.3 (q), 27.4 (t), 41.4 (t), 42.0 (t), 98.4 (d), 99.8 (s), 113.8 (d), 119.6 (d), 124.5–136.6, 143.0 (s), 156.3 (s)	60.9 (60.9)	4.9 (4.9)	6.8 (6.7)

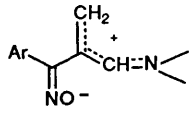
[a] Recrystallisation solvent in parentheses.

Table 4 Preparation of 4-(2-aminobenzyl)isoxazoles **7a–e**

Compd.	Yield (%)	M.p. (°C)	M^+ (*m/z*)	ν_{max}(Nujol)/ cm^{-1}	$\delta_H(CDCl_3)$	Found (%) (Required) C	H	N
7a	30	106–107 (Pr^i_2O)	374	3420	2.08 (6 H, s), 2.60 (3 H, s), 2.79 (3 H, s), 3.30 (1 H, br s), 3.36 (2 H, s), 6.4–6.8 (3 H, m), 7.0–7.2 (1 H, m), 8.30 (1 H, s)	64.0 (64.0)	5.3 (5.4)	7.6 (7.5)
7b	65	88–90 (Pr^i_2O)	388	3410	1.19 (3 H, t, *J* 7), 2.06 (6 H, s), 2.60 (3 H, s), 2.9–3.2 (3 H, overlapping),[a] 3.36 (2 H, s), 6.4–6.7 (3 H, m), 7.0–7.2 (1 H, m), 8.28 (1 H, s)	64.9 (64.8)	5.7 (5.7)	7.3 (7.2)
7c	47	*b*	450	3420	1.95 (6 H, s), 2.60 (3 H, s), 3.38 (2 H, s), 3.68 (1 H, br s), 4.24 (2 H, s), 6.5–6.7 (3 H, m), 6.9–7.3 (6 H, m), 8.20 (1 H, s)			
7d	32	102–104 (Pr^i_2O)	386	3377	1.95 (6 H, s), 2.56 (3 H, s), 2.98 (2 H, t, *J* 6), 3.15 (1 H, br s), 3.31 (2 H, s), 3.40 (2 H, t, *J* 6), 6.54 (2 H, m), 6.96 (1 H, d, *J* 7), 8.35 (1 H, s)	65.0 (65.1)	5.3 (5.2)	7.1 (7.2)
7e	58	157–159 (PhH–hexane)	400	3390	1.7–2.0 (2 H, m), 2.04 (6 H, s), 2.60 (3 H, s), 2.72 (2 H, t, *J* 6), 3.19 (2 H, t, *J* 6), 3.30 (2 H, s), 3.34 (1 H, br s), 6.46 (1 H, t, *J* 8), 6.57 (1 H, d, *J* 8), 6.85 (1 H, d, *J* 8), 8.31 (1 H, s)	65.8 (65.8)	5.6 (5.5)	7.0 (7.0)

[a] After deuteriation: 3.09 (2 H, q, *J* 7). [b] Oil.

carbon,[14] thus directing the carbon of the dipole to attack at this position. The observed regiochemistry may well harmonise with a two-step cycloaddition mechanism *via* the stabilised zwitterionic intermediate **8**. However, such an intermediate is expected to cyclise on both the α- and the γ-position, the latter presumably being preferred on thermodynamic grounds in line with the reported behaviour of dimethylaminoallyl carbocation towards nucleophilic species.[15]



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Finally, the synthetic importance of the rearrangement leading to species **7** must be emphasised. *Prima facie*, one may think that such compounds are accessible by reaction of nitrile oxide **4** with *o*-prop-2-ynylanilines. In reality, this is not so because cycloaddition of nitrile oxides to propargyl derivatives have been amply shown to produce 5-substituted isoxazoles.[16]

Experimental

M.p.s were determined on a Büchi apparatus and are uncorrected. IR spectra were taken on a Perkin-Elmer 1725X FT spectrophotometer. NMR spectra were recorded on a Varian XL-200 instrument; chemical shifts are given in ppm from $SiMe_4$, and *J*-values are given in Hz. Mass spectra were measured on a WG-70EQ apparatus.

Compounds **1a**,[17] **1b**,[17], **1c**,[18] **1d**,[19] **1e**[20] and **4**[21] are known in the literature.

Preparation of Allenes **2a–e**.—A solution of substrate **1** (20 mmol) in tetrahydrofuran (THF) (5 cm^3) was thermostatted at the temperature indicated in Table 1. The proper amount of Bu^tOK was then added to the stirred mixture. After the time given in Table 1, the reaction was quenched by Bu^tOH (1.5 mol equiv. with respect to Bu^tOK). The solvent was removed under reduced pressure, pentane was added (5 cm^3), and the undissolved material was filtered off. The solution was evaporated to give the corresponding allene **2** as an undistillable oil (see Table 1).

Reaction of Allenes **2a–e** *with Nitrile Oxide* **4**.—A solution of an allene **2** (8 mmol) and nitrile oxide **4** (8 or 16 mmol) in tetrachloromethane (40 cm^3) was refluxed for the time indicated in Table 2. After removal of the solvent, the residue was submitted to flash chromatography on a silica gel column. Eluents, products and isolation yields are collected in Table 2. Characteristic data of the products are given in Table 3.

Reaction of Cycloadducts **5a–e** *with Nitrile Oxide* **4**.—A solution of a cycloadduct **5** (0.5 mmol) and nitrile oxide **4** (0.5 mmol) in tetrachloromethane (10 cm^3) was refluxed for 24 h. Evaporation of the solvent left the practically pure corresponding diadduct **6** (NMR analysis).

Isomerisation of Cycloadducts **5a–c**, **e**.—A solution of a cycloadduct **5** (2 mmol) in toluene (30 cm^3) was treated with anhydrous zinc chloride (3 mmol) and refluxed for 1 h. The mixture was poured into water. The organic layer was dried over sodium sulphate. Addition of a small amount of di-isopropyl ether and subsequent filtration gave the practically pure corresponding isoxazole **7** (see Table 4).

Isomerisation of Cycloadduct **5d**.—A solution of cycloadduct **5d** (2 mmol) in toluene (30 cm^3) was treated with anhydrous zinc chloride (4.5 mmol) and refluxed for 2 h. Dichloromethane (30 cm^3) was added and the mixture was poured into water. The organic layer was dried over sodium sulphate and evaporated. The residue was submitted to flash chromatography on a silica gel column with toluene–ethyl acetate (4:1) as eluent to give the isoxazole **7d** (see Table 4).

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