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SUBSTITUENT EFFECTS IN THE INTRAMOLECULAR INVERSE ELECTRON DEMAND DIELS-ALDER REACTIONS OF 5-(P-SUBSTITUTED PHENYL)-2-(1,1-DICYANOPENT-4-YN-1-YL)PYRIMIDINES.

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2-(1,1-dicyanopent-4-yn-1-yl)-5-phenylpyrimidine and some *p*-substituted phenyl derivatives undergo an intramolecular inverse electron demand Diels-Alder reaction to give the corresponding 3-aryl-7,7-dicyano-6,7-dihydro-5*H*-1-pyrindines. A Hammett plot of log k_R/k_H against the known σ values for *p*-substituents reveals a linear relationship with a positive slope $\rho = 0.061$. This result indicates that there is little or no charge separation in the rate determining transition state. Thus, a zwitterionic intermediate can be excluded. The result is also explained in terms of the FMO perturbation theory.

INTRODUCTION

Recently we have described intramolecular inverse electron demand Diels-Alder reactions of pyrimidines carrying an appropriate dienophilic side chain attached to the 2 or the 5 position of the pyrimidine ring[1]. These reactions offer a useful tool to obtain several new annelated pyridines. In this way we have prepared dihydrofuro[2,3-b]-, dihydrothieno[2,3-b]-, dihydrothieno[2,3-c]- and dihydropyrrolo[2,3-b]pyridines[1a,b], 6,7-dihydro-5*H*-1-pyrindines[1c,d], 5,6,7,8-tetrahydroquinolines[1d] and also dihydrofuro[3,4-b]- and dihydrofuro[3,4-c]pyridines[1e]. We have shown that the rate of cycloaddition depends largely upon the nature of the tether between azadiene and dienophile and upon the nature of substituents attached to the pyrimidine or the dienophilic acetylene group. Both electronic and steric effects have been found to influence the reactivity. Our studies thus far have indicated that steric (structural) effects are more important than electronic effects in governing the reactivity towards cycloaddition. Especially, reduction of the degrees of freedom in the chain connecting the dienophilic acetylene group and the azadiene, either by the introduction of bulky substituents at the carbon atom α (and to a lesser degree γ) to the pyrimidine ring[1c-e] or by creating repulsion between lone pairs on the pyrimidine nitrogen atoms and on a β–oxygen atom in the connecting chain[1e], greatly enhances the rate of cycloaddition.

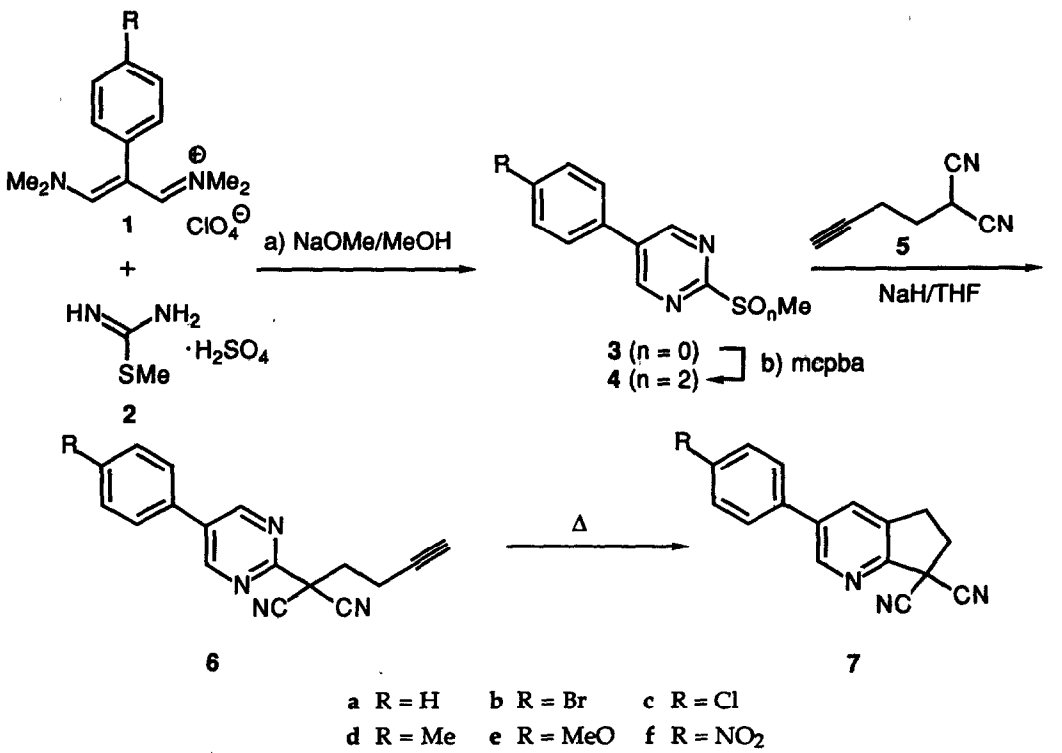
In order to gain further insight into the electronic factors that govern the mechanism of this type of cycloaddition reactions of pyrimidines we looked for a quantitative relationship between the rate of reaction and the electronic influence of substituents on the 5 position of the

azaheterocycle in 2-(1,1-dicyanopent-4-yn-1-yl)pyrimidines. For this reason we prepared the 5-phenyl and a series of 5-(*para*-substituted phenyl) derivatives of 2-(1,1-dicyanopent-4-yn-1-yl)pyrimidine and studied their cycloaddition reaction.

RESULTS AND DISCUSSION

5-Aryl-2-(1,1-dicyanopent-4-yn-1-yl)pyrimidines **6** were synthesized by the methods outlined in Scheme 1. 5-Aryl-2-methylsulfonylpyrimidines **4** were obtained by condensation of the appropriate 2-aryl-1-dimethylamino-3-dimethylimonioprop-1-ene perchlorate **1**[2] with S-methylthiourea sulfate (**2**)[3] and subsequent oxydation of the resulting 5-aryl-2-methylthiopyrimidines **3** with *m*-chloroperoxybenzoic acid. Nucleophilic substitution of the methylsulfonyl group with the sodium salt of 5,5-dicyanopent-1-yne **5**[4] then gave the desired starting materials **6**.

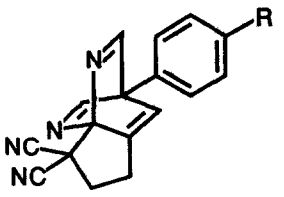
Scheme 1



a R = H **b** R = Br **c** R = Cl
d R = Me **e** R = MeO **f** R = NO_2

The intramolecular Diels-Alder reaction of compounds **6** was performed in nitrobenzene at 180°C under an atmosphere of nitrogen. Under these conditions the cycloaddition into the corresponding 3-aryl-7,7-dicyano-6,7-dihydro-5*H*-1-pyrindines **7** was complete within 1 hour;

the yields were almost quantitative. The structures of all new compounds were established by their ^1H NMR spectra and confirmed by elemental analyses and/or mass spectroscopy.



8

As stated before[1], a tricyclic intermediate cycloadduct **8** is formed by addition of the acetylene group accross the C-2 and C-5 positions of the pyrimidine ring. Such a cycloaddition product could, however, not be isolated or identified by NMR spectroscopy due to the spontaneous cycloreversion into **7** by expulsion of hydrogen cyanide. This indicates that the cycloreversion reaction to the pyrindines is fast and that the rate determining step is the addition of the acetylene group to C-2 and C-5 of the pyrimidine. In order to get more information about the electronic character of the transition state leading to this intermediate cycloadduct we investigated whether a quantitative relationship exists between the rate of cycloaddition and substituents on the C-5 position of the pyrimidine ring. We decided to study the cycloaddition reaction of the afore-mentioned 2-(1,1-dicyanopent-4-yn-1-yl)-5-(*para*-substituted phenyl)pyrimidines **6**, in which the electronic effect of each *para*-substituent is transmitted to the reaction site situated in a constant steric environment. Thus, we should be able to determine a correlation, i.e. a Hammett plot, between the rates of cycloaddition and known[5] σ values for *para*-substituents on the 5-phenyl group.

TABLE 1 Retention times of compounds **6** and **7** under the chromatographic conditions used in this study.

Compound	t_r (min)	Compound	t_r (min)
6a	9.2	**7a**	6.5
6b	16.6	**7b**	11.8
6c	14.9	**7c**	10.3
6d	13.7	**7d**	9.3
6e	9.4	**7e**	6.3
6f	8.3	**7f**	5.9

For these quantitative analyses we used HPLC liquid chromatography with Spherisorb S5 ODS as stationary phase. A mixture of acetonitrile, tetrahydrofuran and water (4 : 1 : 5; v/v) was

found to be convenient to get good separations between the solvent (nitrobenzene), the starting materials (the pyrimidines **6**) and the products (the pyrindines **7**). The retention time of the reaction products **7** was found to be intermediate between that of the solvent peak (t_r = 3.5 min.) and the corresponding starting material **6** (see Table 1).

Our preliminary experiments (see above) revealed that the reactions take place in almost quantitative yield. Therefore, decomposition hardly occurs and the reaction rate can be calculated from the decrease of starting material and the increase of reaction product. The reactions for quantitative analyses were carried out at 140 ± 1°C in nitrobenzene.

First, we monitored the decrease of 2-(1,1-dicyanopent-4-yn-1-yl)-5-(*p*-methoxyphenyl)-pyrimidine (**6e**), using 3-*p*-bromophenyl-7,7-dicyano-6,7-dihydro-5*H*-1-pyrindine (**7b**) as internal standard. As was found earlier for 2- and 5-propynyloxymethylpyrimidines[1e], a plot of $-\ln(C_t/C_0)$ against t revealed that the reaction obeys simple first order kinetics. Thus, the reaction constant (k_{MeO}) for the cycloaddition reaction of **6e** into **7e** could be determined and from this the half-life time ($t_{1/2}$) could be calculated ($k_{MeO} = 0.63 \times 10^{-4}$ s^{-1}; $t_{1/2}$ = 3.06 h). Since cycloreversion from the intermediate tricyclic cycloadduct is fast, these values reflect the rate determining addition of the acetylene group to C-2 and C-5 of the pyrimidine.

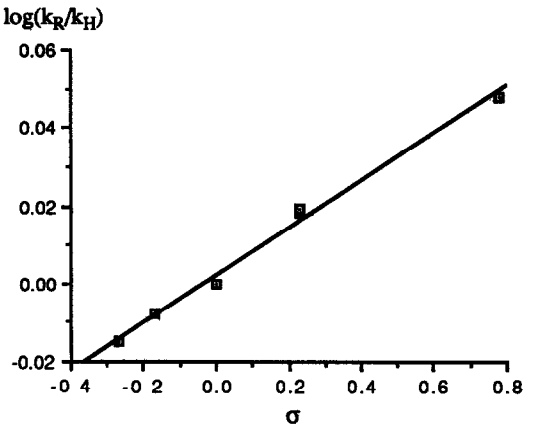
For reasons of accuracy, the reaction constants (k_R) and the half-life times ($t_{1/2}$) of each of the other cycloaddition reactions of 2-(1,1-dicyanopent-4-yn-1-yl)-5-(*para*-substituted phenyl)pyrimidines **6** into their corresponding pyrindine derivatives **7** were determined using the cyclization of the 5-(*p*-bromophenyl) derivative **6b** into its pyrindine derivative **7b** as reference reaction[6]. Thus, we were able to calculate the reaction constant (k_R) for each cycloaddition reaction of **6** into **7** relative to that of **6b** into **7b** (R = Br), thereby eliminating the effect of small fluctuations in reaction temperature on the reaction rate. From the decrease of starting material **6** (entries **a**, **e** and **f**) or the increase of reaction product **7** (entries **c** and **d**) at several time intervals we determined the relative reaction constants k_R/k_{Br} (R = H, Cl, Me, MeO, NO_2) and also k_R/k_H (Table 2). From these data and the independently determined reaction constant (k_{MeO}) for the cyclization of **6e** into **7e** (see above) the reaction constants (k_R) and half-life times ($t_{1/2}$) for the cycloaddition of the other compounds **6** were determined (see Table 2). A Hammett plot of log k_R/k_H

TABLE 2 Relative rates, rate constants and half-life times for the cycloaddition reaction of compounds **6** in nitrobenzene at 140°C.

Compound	R	k_R/k_{Br}	k_R/k_H	$k_R \times 10^{-4}$ s^{-1}	$t_{1/2}$ (h)
6a	H	0.953	1.000	0.65	2.96
6b	Br	1.000	1.049	0.68	2.83
6c	Cl	0.998	1.047	0.68	2.83
6d	Me	0.938	0.984	0.64	3.01
6e	MeO	0.925	0.970	0.63	3.06
6f	NO_2	1.070	1.122	0.73	2.64

against σ values for the *para*-substituents showed a rectilinear relationship (correlation coefficient 0.993) with a positive slope ρ = 0.061 ± 0.003 (Fig. 1).

Figure 1



The positive sign for ρ is in agreement with the inverse electron demand character of this intramolecular Diels-Alder reaction[7,8]. The low value for ρ indicates that in the rate determining transition state leading from **6** to cycloadduct **8** there is hardly any charge separation and thus a two-step reaction via a zwitterionic intermediate can be excluded. This result is generally found for intermolecular Diels-Alder reactions[7] and has now also been found to hold for the intramolecular version.

The magnitude of ρ for the intramolecular Diels-Alder reactions of compounds **6** into **7** (ρ = +0.061) is significantly lower than that for the comparable intermolecular Diels-Alder reaction of *para*-substituted phenyltetrazines (ρ = 1.25)[7]. This low value (ρ = 0.061) indicates that the reaction is less susceptible to polar effects. In terms of frontier molecular orbitals[8,9], the low magnitude of ρ indicates that the mean energy gap between $LUMO_{diene}$ and $HOMO_{dienophile}$ is large as compared to the differences in energy between the successive LUMO's of the diene resulting from changing the *para*-substituent.

We also studied the cyclization reaction of **6e** in solvents less polar than nitrobenzene. It was found (see Table 3) that **6e** cyclizes in nitrobenzene, *p*-bromotoluene and mesitylene with relative rates of 2.3, 1.6 and 1, respectively. The effects of the solvent are small, indicating that the transition state has little or no ionic character. This result lends support to our previous conclusion (see above). Recently, similar solvent effects were found at our laboratory for the intramolecular Diels-Alder reaction of (3-butynylthio)pyrazine[10] and by others for the intermolecular Diels-Alder reaction of 3,6-diphenyl-1,2,4,5-tetrazine with styrene[7]. These differences in reactivity are, however, smaller than in the intermolecular Diels-Alder reaction of 5-nitropyrimidine with electron rich dienophiles, in which case a zwitterionic intermediate has been postulated[11].

TABLE 3 Rate constant and half-life time for the cycloaddition reaction of **6e** into **7e** in different solvents at 140°C.

Solvent	$k \times 10^{-4}\ s^{-1}$	$t_{1/2}$ (h)
nitrobenzene	0.63	3.06
p-bromotoluene	0.45	4.31
mesitylene	0.28	6.97

From the present investigations it can be concluded that the intramolecular Diels-Alder reaction of the 2-alkynylpyrimidines used in our studies indeed have an inverse electron demand character[7]. Furthermore, the electronic influence on the reaction rate is small. This result lends support to our previous conclusions that the observed differences in reaction rate have to be attributed mainly to steric or conformational effects[1d,e].

EXPERIMENTAL SECTION

Melting points are uncorrected. ^1H NMR spectra were recorded on a Varian EM 390 spectrometer. Chemical shifts are determined in ppm downfield from Me_4Si. Mass spectral data were obtained on a AEI MS 902 spectrometer equipped with a VG ZAB console. Column chromatography was performed with Merck silica gel 60 (70 - 230 mesh ASTM).
A Kratos Spectroflow 400 solvent delivery system and a Must Single Valco Injector equipped with a 10 µl sampling loop were used for the HPLC analyses. The detector was a Kratos Spectroflow 773 variable wavelenght spectrophotometer connected to a Hewlett Packard HP3396A Integrator which served also as recorder. The analytical separations were accomplished using a column, 20.0 cm x 4.6 mm, filled with 5 µm Spherisorb S5 ODS. The mobile phase consisted of a mixture of acetonitrile, tetrahydrofuran and water (double distilled) in a ratio of 4 : 1 : 5 (v/v). The flow rate was 1.6 ml/min. The UV detector was operated at 280 nm and the separations were carried out at room temperature.

Starting materials.
2-Aryl-1-dimethylamino-3-dimethylimonioprop-1-ene perchlorates **1** were synthesized as described in the literature[2]. 5-Aryl-2-methylthiopyrimidines **3** were prepared in excellent yields (see Table 4) from the appropriate trimethinium salt **1** and S-methylthiourea sulphate[3] (**2**) by the method described by Wagner and Jutz for 2-methylthio-5-phenylpyrimidine (**3a**)[12]. Melting points and ^1H NMR spectra of compounds **3a-e** were all in agreement with those reported in the literature[13]. In the same way compound **3f** was obtained from 1-dimethylamino-3-dimethylimonio-2-(*p*-nitrophenyl)prop-1-ene perchlorate[2a] (**1f**).
2-Methylthio-5-(*p*-nitrophenyl)pyrimidine (**3f**). Obtained as a pale yellow solid. Yield: 65%; m.p. 211-214°C (hexane/chloroform). ^1H NMR ($CDCl_3$) δ 8.77 (s, 2H), 8.35 (d, J = 8.7 Hz, 2H), 7.72 (d, J = 8.7 Hz, 2H), 2.61 (s, 3H). Anal. Calcd. for $C_{11}H_9N_3O_2S$ (247.28): C, 53.42; H, 3.66; N, 16.99. Found: C, 53.14; H, 3.56; N, 17.00.
Oxidation of compounds **3** to the analogous 5-aryl-2-methylsulfonylpyrimidines **4** with *m*-chloroperoxybenzoic acid was performed according to the procedure described in literature[13].

Table 4 Synthesis of 5-aryl-2-methylthiopyrimidines 3.

Compound	R	% yield
3a	H	81
3b	Br	96
3c	Cl	93
3d	Me	95
3e	MeO	90
3f	NO_2	65

General procedure for the synthesis of 5-aryl-2-(1,1-dicyanopent-4-yn-1-yl)pyrimidines 6.
To a stirred suspension of sodium hydride (84 mg; 2.8 mmole, 80% oil dispersion) in anhydrous tetrahydrofuran (5 ml) was added at room temperature 5,5-dicyanopent-4-yne[4] (330 mg; 2.8 mmole). After the initial effervescence had subsided, the appropriate 5-aryl-2-methylsulfonylpyrimidine (2.5 mmole) was added in one portion and the reaction mixture was refluxed for two hours. After cooling water was added and the aqueous layer extracted twice with dichloromethane. The combined organic layers were washed with water, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Column chromatography (eluting with dichloromethane/petroleum ether 40/60 5:1) of the residue afforded the desired products.

2-(1,1-Dicyanopent-4-yn-1-yl)-5-phenylpyrimidine (6a). From 2-methylsulfonyl-5-phenylpyrimidine (4a). Obtained as a colourless solid (91%): m.p. 97-98°C (hexane/toluene); ^1H NMR ($CDCl_3$) δ 9.00 (s, 2H), 7.55 (s, 5H), 2.9-2.4 (mc, 4H), 1.97 (t, J = 2.4 Hz, 1H). MS: m/e 272 (M^+).
Anal. Calcd. for $C_{17}H_{12}N_4$ (272.30): C, 74.97; H, 4.44; N, 20.57. Found: C, 74.93; H, 4.44; N, 20.64.

5-*p*-Bromophenyl-2-(1,1-dicyanopent-4-yn-1-yl)pyrimidine (6b). From 5-*p*-bromophenyl-2-methylsulfonylpyrimidine (4b). Obtained as a colourless solid (97%): m.p. 128-129°C (hexane/toluene); ^1H NMR ($CDCl_3$) δ 9.00 (s, 2H), 7.71 (d, J = 8.7 Hz, 2H), 7.47 (d, J = 8.7 Hz, 2H), 2.9-2.4 (mc, 4H), 1.98 (t, J = 2.7 Hz, 1H).
Anal. Calcd. for $C_{17}H_{11}BrN_4$ (351.21): C, 58.13; H, 3.15; N, 15.95. Found: C, 58.28; H, 3.11; N, 15.82.

5-*p*-Chlorophenyl-2-(1,1-dicyanopent-4-yn-1-yl)pyrimidine (6c). From 5-*p*-chlorophenyl-2-methylsulfonylpyrimidine (4c). Obtained as a colourless solid (88%): m.p. 134-135°C (hexane/toluene; ^1H NMR ($CDCl_3$) δ 8.98 (s, 2H), 7.52 (s, 4H), 2.9-2.4 (mc, 4H), 1.96 (t, J = 2.7 Hz, 1H).
Anal. Calcd. for $C_{17}H_{11}ClN_4$ (306.75): C, 66.55; H, 3.61; N, 18.26. Found: C, 66.38; H, 3.58; N, 18.53.

2-(1,1-Dicyanopent-4-yn-1-yl)-5-*p*-methylphenylpyrimidine (6d). From 5-*p*-methylphenyl-2-methylsulfonylpyrimidine (4d). Obtained as a colourless solid (79%): m.p. 78-79°C (hexane/toluene); ^1H NMR ($CDCl_3$) δ 8.98 (s, 2H), 7.49 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 2.9-2.4 (mc, 4H), 2.42 (s, 3H), 1.97 (t, J = 2.7 Hz, 1H).
Anal. Calcd. for $C_{18}H_{14}N_4$ (286.32): C, 75.50; H, 4.92; N, 19.56. Found: C, 75.56; H, 4.83; N, 19.33.

2-(1,1-Dicyanopent-4-yn-1-yl)-5-*p*-methoxyphenylpyrimidine (6e). From 5-*p*-methoxyphenyl-2-methylsulfonylpyrimidine (4e). Obtained as a colourless solid (77%): m.p. 111-112°C (hexane/toluene); ^1H NMR ($CDCl_3$) δ 8.97 (s,2H), 7.52 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H), 2.9-2.4 (mc, 4H), 1.97 (t , J = 2.4 Hz, 1H).

Anal. Calcd. for $C_{18}H_{14}N_4O$ (302.32): C, 71.50; H, 4.66; N, 18.53. Found: C, 71.53; H, 4.64; N, 18.61.

2-(1,1-Dicyanopent-4-yn-1-yl)-5-*p*-nitrophenylpyrimidine (6f). From 2-methylsulfonyl-5-*p*-nitrophenylpyrimidine (4f). Obtained as a yellow solid (87%): m.p. 169-174°C (with decomposition; hexane/toluene); ^{1}H NMR ($CDCl_3$) δ 9.08 (s, 2H), 8.44 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.9 Hz, 2H), 2.9-2.4 (mc, 4H), 1.97 (t, J = 2.7 Hz, 1H).
Anal. Calcd. for $C_{17}H_{11}N_5O_2$ (317.30): C, 64.34; H, 3.49; N, 22.07. Found: C, 64.34; H, 3.44; N, 22.05.

General procedure for the intramolecular Diels-Alder reaction of 5-aryl-2-(1,1-dicyanopent-4-yn-1-yl)pyrimidines 6 to 3-aryl-7,7-dicyano-6,7-dihydro-5*H*-1-pyrindine 7.
The appropriate pyrimidine derivative (1.0 mmole) was dissolved in nitrobenzene (100 mg/1 ml solvent) and heated at 180°C under nitrogen for one hour. After cooling the reaction mixture was chromatographed over silica gel. Eluting first with dichloromethane to remove nitrobenzene, then dichloromethane/ether 4:1 gave the reaction products.

7,7-Dicyano-6,7-dihydro-3-phenyl-5*H*-1-pyrindine (7a). From **6a**. **7a** Was obtained as a colourless solid (100%): m.p. 134-135°C (hexane/toluene); ^{1}H NMR ($CDCl_3$) δ 8.74 (br s, 1H), 7.84 (t, J = 1.0 Hz, 1H), 7.50 (mc, 5H), 3.27 (br t, J = 6.1 Hz, 2H), 3.00 (mc, 2H). MS: m/e 245 (M^+).
Anal. Calcd. for $C_{16}H_{11}N_3$ (245.27): C, 78.34; H, 4.52; N, 17.13. Found: C, 78.10; H, 4.43; N, 17.01.

3-*p*-Bromophenyl-7,7-dicyano-6,7-dihydro-5*H*-1-pyrindine (7b). From **6b**. **7b** Was obtained as a colourless solid (99%): m.p. 151-152°C (hexane/toluene); ^{1}H NMR ($CDCl_3$) δ 8.72 (br s, 1H), 7.83 (t , J = 1.0 Hz, 1H), 7.64 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 8.7 Hz, 2H), 3.29 (br t, J = 6.2 Hz, 2H), 3.01 (mc, 2H).
Anal. Calcd. for $C_{16}H_{10}BrN_3$ (324.18): C, 59.27; H, 3.10; N, 12.96. Found: C, 59.06; H, 3.11; N, 12.89.

3-*p*-Chlorophenyl-7,7-dicyano-6,7-dihydro-5*H*-1-pyrindine (7c). From **6c**. **7c** Was obtained as a colourless solid (97%): m.p. 147-148°C (hexane/toluene); ^{1}H NMR ($CDCl_3$) δ 8.73 (br s, 1H), 7.84 (br s, 1H), 7.49 (s, 4H), 3.29 (mc, 2H), 3.01 (mc, 2H).
Anal. Calcd. for $C_{16}H_{10}ClN_3$ (279.72): C, 68.69; H, 3.60; N, 15.02. Found: C, 68.47; H, 3.55; N, 15.00.

7,7-Dicyano-6,7-dihydro-3-*p*-methylphenyl-5*H*-1-pyrindine (7d). From **6d**. **7d** Was obtained as a colourless solid (100%): m.p. 119-121°C (hexane/toluene); ^{1}H NMR ($CDCl_3$) δ 8.75 (br s, 1H), 7.84 (br s, 1H), 7.46 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 3.27 (mc, 2H), 2.99 (mc, 2H), 2.41 (s, 3H).
Anal. Calcd. for $C_{17}H_{13}N_3$ (259.30): C, 78.73; H, 5.05; N, 16.20. Found: C, 78.58; H, 5.03; N, 16.11.

7,7-Dicyano-6,7-dihydro-3-*p*-methoxyphenyl-5*H*-1-pyrindine (7e). From **6e**. **7e** Was obtained as a colourless solid (98%): m.p. 144-146°C (hexane/toluene); ^{1}H NMR ($CDCl_3$) δ 8.73 (br s, 1H), 7.81 (t, J = 1.0 Hz, 1H), 7.48 (d, J = 8.7 Hz, 2H), 7.02 (d, J = 8.7 Hz, 2H), 3.84 (s, 3H), 3.26 (mc, 2H), 2.99 (mc, 2H).
Anal. Calcd. for $C_{17}H_{13}N_3O$ (275.30): C, 74.16; H, 4.75; N, 15.26. Found: C, 74.13; H, 4.69; N, 14.96.

7,7-Dicyano-6,7-dihydro-3-*p*-nitrophenyl-5*H*-1-pyrindine (7f). From **6f**. **7f** Was obtained as a pale yellow solid (100%): m.p. 205-208°C (hexane/toluene); ^{1}H NMR ($CDCl_3$) δ 8.83 (br s, 1H), 8.38 (d, J = 9.0 Hz, 2H), 7.94 (br s, 1H), 7.75 (d, J = 9.0 Hz, 2H), 3.34 (mc, 2H), 3.06 (mc, 2H).
Anal. Calcd. for $C_{16}H_{10}N_4O_2$ (290.27): C, 66.20; H, 3.47; N, 19.30. Found: C, 65.80; H, 3.40; N, 19.33.

Kinetic measurements.

a. Solvent effects. Weighed amounts of the pyrimidine **6e** and pyrindine **7e** (± 15 mg for each) were dissolved in the appropriate solvent (0.6 ml). This reaction mixture was heated at 140 ± 1°C in a stoppered flask on an oil bath and after several time intervals a sample was taken for quantitative analysis. For this purpose the sample was diluted with acetonitrile (± 5 ml) and the decrease of starting material was determined by HPLC analysis using compound **7b** as internal standard[14]. From a plot of $-\ln(C_t/C_0)$ against time the reaction constant (k_{MeO}) and the half-life time were calculated (see Table 3).

b. Substituent effect. Weighed amounts (± 15 mg for each) of a pyrimidine **6** (R = H, Cl, Me, MeO, NO_2), pyrimidine **6b** and 3-phenyl-5*H*[1]benzopyrano[4,3-b]pyridine[15], which served as internal standard in the HPLC analysis, were dissolved in 0.6 ml of nitrobenzene. The reaction mixture was heated at 140°C and after several time intervals a sample was taken, diluted with acetonitrile (± 5 ml) and subjected to quantitative analysis by means of HPLC. The decrease of starting material **6** (entries **a**, **e** and **f**) relative to **6b** or the increase of reaction product **7** (entries **c** and **d**) relative to **7b** was determined. These data were used to calculate the relative reaction constants k_R/k_{Br} and k_R/k_H (see Table 2).

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REFERENCES AND NOTES

1a. A.E. Frissen, A.T.M. Marcelis and H.C. van der Plas, *Tetrahedron Lett.*, **1987**, *28*, 1589.
b. A.E. Frissen, A.T.M. Marcelis and H.C. van der Plas, *Tetrahedron*, **1989**, *45*, 803.
c. A.E. Frissen, A.T.M. Marcelis, G. Geurtsen, D.A. de Bie and H.C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, **1987**, *106*, 547.
d. A.E. Frissen, A.T.M. Marcelis, G. Geurtsen, D.A. de Bie and H.C. van der Plas, *Tetrahedron*, **1989**, in press.
e. A.E. Frissen, A.T.M. Marcelis, D.G. Buurman, C.A.M. Pollmann and H.C. van der Plas, *Tetrahedron*, **1989**, in press.
2a. Z. Arnold, *Collect. Czech. Chem. Commun.*, **1961**, *26*, 3091. *Chem. Abstr.*, **1962**, *56*, 15328g.
b. A. Holy, J. Krupicka and Z. Arnold, *Collect. Czech. Chem. Commun.*, **1965**, *30*, 4127.
c. C. Jutz, R. Kirchlechner and H.-J. Seidel, *Chem. Ber.*, **1969**, *102*, 2313.
3. P.R. Shildneck and W. Windus, *Org. Syntheses*, **1932**, *12*, 52.
4a. E.C. Taylor and J.E. Macor, *Tetrahedron Lett.*, **1986**, *27*, 2107.
b. J.E. Macor, *Ph D. Thesis*, Princeton University, **1986**, p 297.
5. H.H. Jaffé, *Chem. Rev.*, **1953**, *53*, 191.
6. The conversion of **6b** into **7b** was chosen as reference reaction because good separations were obtained between these 2 compounds and all other compounds **6** and **7** (see Table 1).

7. J. Sauer and R. Sustmann, *Angew. Chem.*, **1980**, *92*, 773.
8. O. Henri-Rousseau and F. Texier, *J. Chem. Ed.*, **1978**, *55*, 437.
9. A.A. Broekhuis, J.W. Scheeren and R.J.F. Nivard, *Recl. Trav. Chim. Pays-Bas*, **1981**, *100*, 143.
10. D.A. de Bie, A. Ostrowicz, G. Geurtsen and H.C. van der Plas, *Tetrahedron*, **1988**, *44*, 2977.
11a. H.C. van der Plas, A.T.M. Marcelis, D.M.W. van den Ham and J.W. Verhoeven, *J. Org. Chem.*, **1986**, *51*, 4070.
b. A.T.M. Marcelis and H.C. van der Plas, *Tetrahedron*, **1989**, *45*, 2693.
12. R. Wagner and C. Jutz, *Chem. Ber.*, **1971**, *104*, 2975.
13. D.J. Brown and B. England, *J Chem. Soc. (C)*, **1971**, 425.
14. The retention times (t_r) for the solvents nitrobenzene, *p*-bromotoluene and mesitylene on the *HPLC* column used are *3.5* min., *11.9* min. and *15.8* min., respectively.
15. This compound was prepared at our laboratory by an intramolecular Diels-Alder reaction of 5-phenyl-2-(2-prop-2-ynyloxyphenyl)pyrimidine. The retention time (t_r) of this compound on the HPLC column used was 17.8 min.