Substituent Effects in the Cycloaddition Reactions of Reissert Hydrofluoroborate Salts with Alkenes

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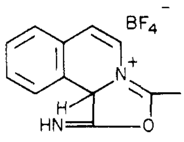
An evaluation of substitutent effects has been undertaken of the cycloaddition of 2-aroyl-1,2-dihydroisoquinaldonitrile hydrofluoroborates (**5**) with substituted ethyl cinnamates, styrenes, stilbenes, and ethylenes. The cinnamates give mixtures of 2-(1-isoquinolyl)-3,5-diaryl-4-carbethoxypyrroles. The stilbenes give mixtures of 2-(1-isoquinolyl)-3,4,5-triarylpyrroles, but the styrenes give only 2-(1-isoquinolyl)-3,5-diarylpyrroles. 1-Hexene and cyclohexene undergo cycloaddition with **5** (Y = H) readily, but 2-heptene does not. The rates of many of these reactions have been determined. The implications of the results with respect to the mechanism of reaction are discussed.

Dewar, Olivella, and Rzepa[2] have carried out theoretical studies which indicate that the lowest pathway for the Diels–Alder reaction of 1,3-butadiene with ethylene to form cyclohexene involves two transition states separated by a biradicaloid intermediate. Later theoretical studies[3] of the other major type of (2 + 4) cycloaddition, viz., the 1,3-dipolar addition reaction (in the case of acetylene with fulminic acid to form isoxazole), indicate the transition state to be relatively symmetric, but the stretching force constants of the two new bonds being formed in the transition state differ by a factor of 10. Thus, the possibility that an unstable biradicaloid intermediate is also formed in this reaction cannot be ruled out. Finally, Bartlett and his co-workers[4] have prepared a highly hindered alkene which, for steric reasons, cannot undergo a synchronous (2 + 4) cycloaddition reaction with phenyl azide. Nevertheless, a cycloaddition reaction of these reagents does occur and almost as rapidly as that between an isomeric alkene, one which is sterically capable of undergoing a synchronous (2 + 4) cycloaddition, and phenyl azide. This suggests that the formation of an unstable biradicaloid intermediate occurs, at least in the former reaction and perhaps in all such reactions. Thus, the controversy between Huisgen[5] and Firestone[6] about the mechanism of the 1,3-dipolar addition reaction is now tipped in favor of Firestone, and since many orientation effects and at least some kinetics data in 1,3-dipolar and Diels–Alder reactions are readily explained by invoking the concept of the formation of unstable biradicaloid intermediates, we will make use of this concept in explaining the results of our most recent studies of the cycloaddition reactions of Reissert hydrofluoroborate salts with alkenes.



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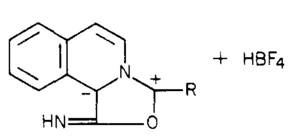

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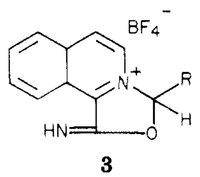

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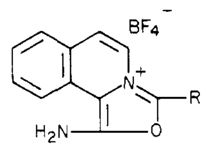

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Evidence has been presented that solutions of the hydrofluoroborate salts of 2-acyl-1,2-dihydroisoquinaldonitriles (Reissert compounds) consist of equilibrium mixtures of **1**, **3**, and **4**, the latter being the major component.[7,8] These salts are also presumed to be in equilibrium with the original[9] Reissert compound, the 1,3-dipolar compound **2** (a mesoionic compound), and fluoroboric acid. Several studies of 1,3-dipolar addition reactions of hydrofluoroborate salts of Reissert compounds have been reported.[10-14] Numerous examples of complex, acid-catalyzed, condensation–rearrangement reactions of Reissert compounds with olefins have also been reported.[15-19] It is believed that these condensation–rearrangement reactions involve an initial Diels–Alder type of cycloaddition of the olefin to the isomeric form **4** of the Reissert salt, and detailed mechanisms of reaction have been suggested.[10,17-19]

An evaluation of substituent effects has now been undertaken of the cycloaddition of 2-aroyl-1,2-dihydroisoquinaldonitrile hydrofluoroborates (**5**) with (1) substituted ethyl cinnamates (**6**), (2) substituted styrenes, (3) substi-

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[1] (a) University of Massachusetts. (b) Universidad Simon Bolivar.

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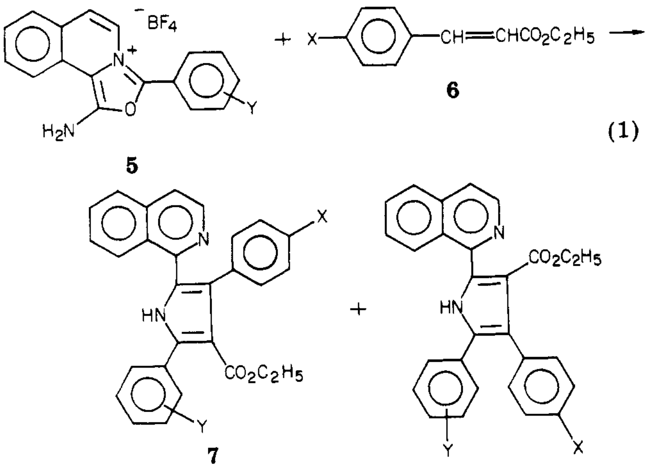
tuted stilbenes, and (4) aliphatic alkenes. The results of each of these series of reactions will be presented individually.

Discussion

Cycloaddition reactions of 2-aroyl-1,2-dihydroisoquinaldonitrile hydrofluoroborates (**5**) with substituted ethyl cinnamates (**6**) were carried out in dimethylformamide solution at room temperature and were found to give mixtures of two isomeric isoquinolylpyrroles of types **7** and **8** (eq 1). In all cases, no matter what the substituents were, the isoquinolylpyrrole of type **7** was always the major product and that of type **8** the minor. However, the ratios of the isomers differed considerably, depending on the substituent. Normally, the major product of type **7** could be isolated in pure form from the mixture of isomers, but the isomer of type **8** could not. The only instance where **8** rather than **7** was isolated in pure form was when Y = p-OCH$_3$ and X = H.



(1)

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That the isoquinolylpyrroles of types **7** and **8** probably arise by an initial Diels–Alder addition of the substituted ethyl cinnamates (**6**) to the 2-aroyl-1,2-dihydroisoquinaldonitrile hydrofluoroborates (**5**) is indicated by the nature of the substituent effects, particularly in the observation of a small positive ρ (=1.24) value for the Hammett plot, as revealed by the data from kinetics studies. The results of these reactions are summarized in Table I.

Cycloaddition reactions of 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate with substituted styrenes were carried out in dimethylformamide solution at 95–100 °C and were found to give isoquinolylpyrroles of type **9**. The results are summarized in Table II.

Table I. Cycloaddition Reactions of 2-Aroyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborates (5) with Substituted Ethyl Cinnamates (6)

reagents		% yield		10^5k_2,[a]
Y for 5	X for 6	7	8	$L^2\ mol^{-2}\ s^{-1}$
H	NO$_2$	57.0	5.0	126.20
H	H	43.4	21.6	20.85
H	Me	18.0	7.0	7.39
H	OMe	16.6	7.2	6.31
m-F	H	18.6	9.3	55.05
p-OMe	H	19.9	9.1	5.97

[a] DMF, 32.7 ± 0.1 °C.

Table II. Cycloaddition Reactions of 2-Benzoyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (4, R = C$_6$H$_5$) with Substituted Styrenes, p-XC$_6$H$_4$CH=CH$_2$, in DMF for 24 h

X	temp, °C	no. of equiv of XC$_6$H$_4$-CH=CH$_2$	% yield of 9
H	100	2	48
H	100	5	58
H	120	5	33
Cl	100	5	44
Me	100	5	52
OMe	100	5	30
NO$_2$	100	5	38

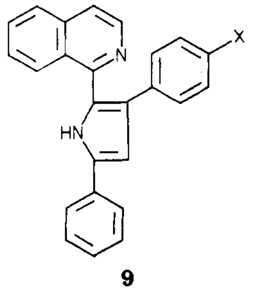
Table III. Relative Reactivities of p-XC$_6$H$_4$CH=CH$_2$ toward 4 (R = Phenyl) in DMF at 100 °C

X	$k_X/k_{p\text{-Me}}$	k_X/k_0
Cl	1.95	1.44
H	1.35	1.00
Me	1.00	0.74
OMe	0.83	0.61

Table IV. Cycloaddition Reactions of 2-Benzoyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (4, R = C$_6$H$_5$) with *trans*-p-XC$_6$H$_4$CH=CHC$_6$H$_5$ in DMF at 100 °C for 24 h

	% yield	
X	11	10
NMe$_2$	23	0[a]
OMe	18	9
Me	21	9
H	34	
Cl	35	0[a]
NO$_2$	45	0[a]

[a] Trace amounts presumably formed.



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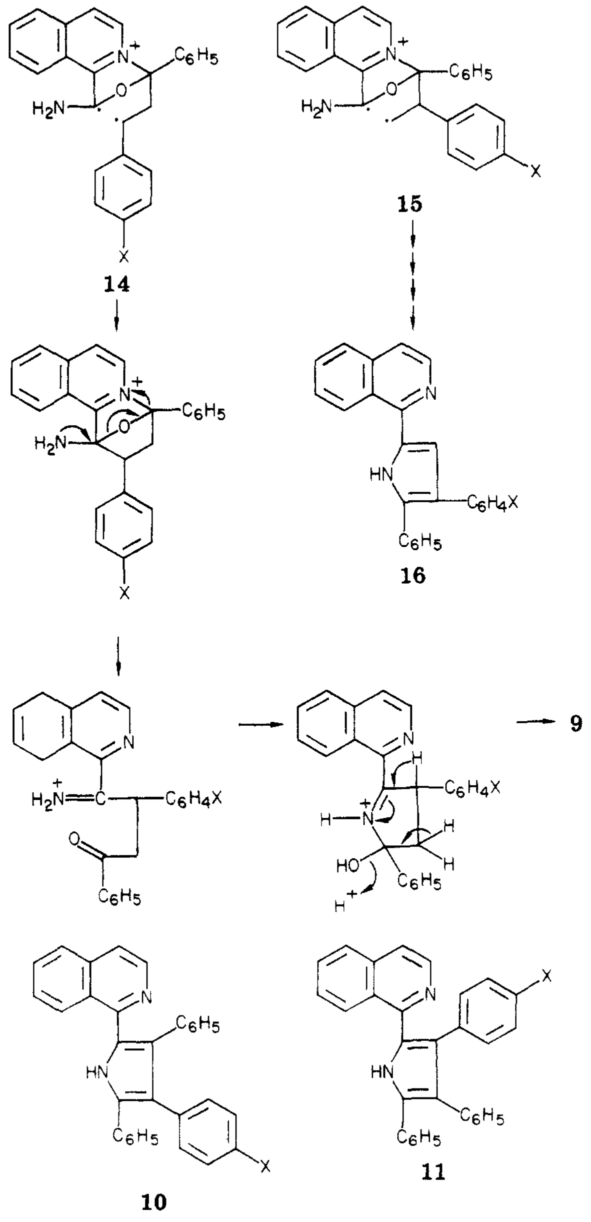
Competition reactions in which 1 equiv of **4** (R = C$_6$H$_5$) was caused to react with 5 equiv of p-methylstyrene and 5 equiv of each of the other styrenes in DMF at 100 °C for 24 h were carried out, and the product mixtures were analyzed by a combination of column chromatography and NMR spectroscopy. The relative rates of reaction of the styrenes (Table III) could be correlated by use of the Hammett equation. The small, positive value of ρ (+0.74) is consistent with the results of known Diels–Alder reactions, and, as in the case of the substituted ethyl cinnamates, this is taken as evidence for an initial cycloaddition step of this type.

The results of the reactions of substituted stilbenes with **4** (R = C$_6$H$_5$) in DMF solution at 95–100 °C, to give products of types **10** and **11**, are summarized in Table IV.

The most striking feature of the data presented in Table IV is that the pyrrole isomer **11** with the substituted phenyl group attached to the 3-carbon is the predominant isomer in every case, regardless of whether the substituent is electron donating or withdrawing. It is obvious that this result cannot be attributed to steric factors.

Firestone[6] contends that, in a case where steric factors

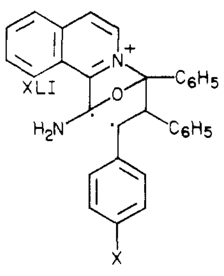
Scheme I



are essentially constant, the electronic factors should direct the course of a concerted 1,3-dipolar (or Diels–Alder) cycloaddition toward that orientation in which the more electrophilic end of the dipolarophile links with the negative end of the dipole. It is also clear that a two-step ionic mechanism involving a dipolar intermediate would give predominantly one isomer when reaction occurs with a dipolarophile substituted with an electron-withdrawing group and the opposite isomer when reaction occurs with a dipolarophile substituted with an electron-donating group.

To explain the cases where only one isomer results, Firestone proposes a two-step mechanism involving a spin-paired diradical as the intermediate where closure to products and reversion to reactants are both faster than rotation about bonds.

Since two-step diradical mechanisms for certain Diels–Alder reactions have been proposed before,[20,21] it seems reasonable that the above theory for 1,3-dipolar reactions could be extended to the initial Diels–Alder reaction between 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate and substituted stilbenes as a possible explanation for the observed data. According to Firestone's theory, the type of diradical shown (**12**) is the intermediate which is necessary to explain the formation of the major products, which are the 3-*p*-XC_6H_4 pyrroles.



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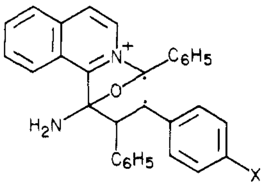
The minor products, the 4-*p*-XC_6H_4 pyrroles, must then be formed via a diradical of type **13**.



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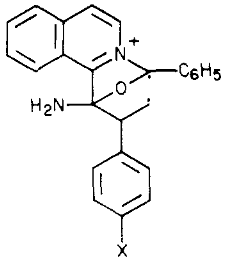
Firestone is careful to point out that little is known about factors governing radical stability, making it very difficult ordinarily to determine which of the possible diradical intermediates is the most stable. This makes it virtually impossible to predict the major products in advance in most instances. This would certainly be true of the intermediates **12** and **13** (and their isomers) and of the corresponding intermediates in the ethyl cinnamate cycloaddition reactions. However, in the case of the styrene addition reactions, the situation is quite different. The exclusive (or, at least, highly predominant) product **9** would arise from the spin-paired diradical **14**, which is clearly of lower energy content than the alternative intermediate **15** (which would lead to the isomeric product **16**, which was not detected in any of the styrene reactions; Scheme I).

The possible, isomeric, spin-paired diradicals **17** and **18** must also be considered. Diradical **17**, which would give



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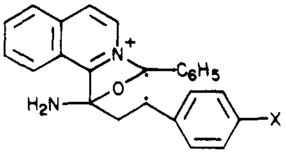

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the actual product, **9**, would not be formed as readily as **14** on the basis of delocalization energy considerations, while **18**, which would have a greater delocalization energy

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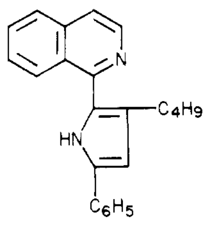
Table V. Cycloaddition Reactions of 2-Benzoyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (4, R = C_6H_5) with Aliphatic Alkenes in DMF

alkene	time, h	temp, °C	% yield (product)
1-hexene	27	25	42 (44)
1-hexene	6	25	30 (44)
1-hexene	6	0	4.5 (44)
1-hexene	6	−20	2.0 (44)
cyclohexene	36	25	37 (45)
cyclohexene	6	25	9.4 (45)
cyclohexene	6	−20	0.1 (45)
2-heptene	72	80	2.0[a]
2-heptene	6	25	0.0
styrene	6	−20	48 (31, X = H)

[a] Mixture of isomeric cycloaddition products.

than 17 (but would lead to the wrong product, 16) is of higher energy than 14 for steric reasons (adjacent aryl groups). Thus, the spin-paired diradical intermediate hypothesis leads to the correct prediction that 9 should be formed preferentially by way of 14.

That steric considerations can play a major role in the cycloaddition reactions of alkenes with Reissert hydrofluoroborate salts is apparent from the data presented in Table V. Reactions of 4 (R = C_6H_5) with 1-hexene and cyclohexene at 25 °C in DMF produce compound 44 and 45 (see Table VI), respectively, with approximately equal ease, but 2-heptene undergoes reaction with 4 (R = C_6H_5) only to a slight degree, even when the reaction mixture is heated to 80 °C. A mixture of isomeric isoquinolylpyrroles is produced in the latter reaction. Once again, the concept of the formation of spin-paired diradicals as intermediates plus steric considerations appear to be capable of rationalizing these results.



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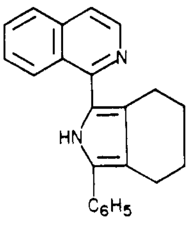

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The structures of most of the products mentioned above have been proved by unambiguous independent syntheses. Other structures were assigned on the basis of spectral evidence and analogy. Reaction data and physical properties of the products are provided in Table VI.

In conclusion, although we have cited some theoretical and experimental evidence which suggests that the concept of the formation of an unstable biradicaloid intermediate in the initial step of the reactions described herein provides a clearer rationalization of the data than the alternative concept of a synchronous (2 + 4) cycloaddition reaction, we have offered no definitive proof of this. Furthermore, a recent, new adaptation[25] of frontier orbital theory as applied to complex Diels–Alder reactions may eventually supplant both of the above concepts, as presently utilized.

Experimental Section

(A) Preparation of Reissert Hydrofluoroborate Salts. 2-Benzoyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate. This compound, mp 196-198 °C dec, was prepared as described previously.[12]

2-(*m*-Fluorobenzoyl)-1,2-dihydroisoquinaldonitrile. The compound was prepared according to the method of Popp and Soto[22] in 13% yield and was recrystallized from 95% ethanol: mp 156–158 °C; NMR ($CDCl_3$) δ 6.08 (d, 1 H, J = 8.0 Hz), 6.54 (s, 1 H), 6.61 (d, 1 H, J = 8.0 Hz), 7.35 (m, 8 H).

Anal. Calcd for $C_{17}H_{11}FN_2O$: C, 73.37; H, 3.99; F, 6.83; N, 10.07. Found: C, 73.25; H, 3.99; F, 6.80; N, 10.05.

2-(*m*-Fluorobenzoyl)-1,2-dihydroisoquinaldonitrile Hydrofluoroborate. This compound was prepared according to the method previously described:[12] 81% yield; mp 189-191 °C; IR ($CHCl_3$) 3440, 3320, 1630, 1600, 1585, 1202, 1015, 858, 765 cm^{-1}; NMR (Me_2SO-d_6) δ 7.30–8.60 (m).

Anal. Calcd for $C_{17}H_{12}BF_5N_2O$: C, 55.77; H, 3.31; F, 25.95; N, 7.65. Found: C, 56.07; H, 3.60; F, 25.71; N, 7.78.

2-(*p*-Anisoyl)-1,2-dihydroisoquinaldonitrile. This compound was prepared according to the method of Weinstock and Boekelheide;[23] mp 173–174 °C (lit.[23] mp 173–174 °C).

2-(*p*-Anisoyl)-1,2-dihydroisoquinaldonitrile Hydrofluoroborate. This compound was prepared according to the method previously described;[12] mp 210–212 °C dec (lit.[12] mp 210–212 °C dec).

(B) Reactions of Reissert Hydrofluoroborate Salts with Olefins. In all cases, the procedure utilized for the reaction between the Reissert salt and styrene was used.[14] For each pyrrole prepared by this method, spectral evidence, elemental analysis, the melting point, reaction conditions, and the percent yield are reported in Table VI. In some cases, the structure of the pyrrole was further verified by unambiguous independent synthesis. In such cases, where synthetic proofs were previously carried out, appropriate references are given in the tables. New work is reported in the following sections of this experimental section. For the pyrroles, N-H peaks were not reported, but they are ordinarily found in the range δ 10–14. Addition of 1 drop of deuterated water to the solution resulted in all cases in the disappearance of the broad N-H peak.

All alkenes used in the preparation of the pyrroles are either available commercially or are known compounds which were synthesized by known procedures.

(C) Proofs of Structure by Independent Synthesis. Ethyl 2-(1-Isoquinolyl)-3-(*p*-nitrophenyl)-5-phenylpyrrole-4-carboxylate (19). Treatment of this pyrrole with stannous chloride in a mixture of glacial acetic acid and hydrochloric acid resulted in the formation of the corresponding amino derivative. Diazotization and reduction of the resulting diazonium salt with hypophosphorous acid gave ethyl 3,5-diphenyl-2-(1-isoquinolyl)pyrrole-4-carboxylate (21), whose structure had been proved previously in an unambiguous manner.[19]

Ethyl 2-(1-Isoquinolyl)-3-(*p*-anisyl)-5-phenylpyrrole-4-carboxylate (25). This compound was synthesized independently by causing the diazonium salt derived from 19 to undergo methanolysis in situ by the addition of an excess of methanol.

2-(1-Isoquinolyl)-3-[*p*-(dimethylamino)phenyl]-4,5-diphenylpyrrole (36). Two treatments of the tertiary amine 36 with manganese dioxide, with subsequent acid-catalyzed hydrolysis, produced the corresponding primary amine. Diazotization followed by methanolysis in situ gave the known compound 37.[15]

2-(1-Isoquinolyl)-3-(*p*-chlorophenyl)-4,5-diphenylpyrrole (42). This compound was synthesized independently by treatment of the diazonium salt derived from 43 with cuprous chloride.

2-(1-Isoquinolyl)-3-(*p*-nitrophenyl)-4,5-dyphenylpyrrole (43). Treatment of this pyrrole with stannous chloride in a mixture of glacial acetic acid and hydrochloric acid resulted in the formation of the corresponding amino derivative. Diazotization followed by methanolysis in situ gave the known compound 37.[15]

(D) Competition Reactions of the Reissert Salt, 2-Benzoyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate, with Substituted Styrenes. Competition reactions in which 1 equiv of the Reissert salt was caused to react with 5 equiv of *p*-methylstyrene and 5 equiv of each of the other styrenes in DMF at 100 °C for 24 h were carried out. The mixture of the pyrroles formed in each reaction was isolated by column chromatography and then analyzed by NMR spectroscopy. The relative yields of the pyrroles formed and, therefore, the relative reactivities toward the Reissert salt were determined in each case by com-

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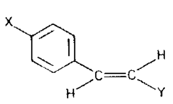
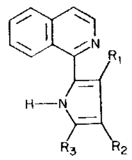
Table VI. Reactions of Reissert Hydrofluoroborate Salts with Olefins[a]



olefin



product

X	Y	no.	R$_1$	R$_2$	R$_3$	mp, °C	yield, %	conditions	NMR (CDCl$_3$), δ (*J*, Hz)
NO$_2$	CO$_2$C$_2$H$_5$	**19**[b]	*p*-O$_2$NC$_6$H$_4$	CO$_2$C$_2$H$_5$	C$_6$H$_5$	224–225	57	DMF, 100 °C, 19 h	1.0 (t, 3 H, *J* = 7.0), 4.1 (q, 2 H, *J* = 7.0), 7.5 (m, 15 H)
		20	CO$_2$C$_2$H$_5$	*p*-O$_2$NC$_6$H$_4$	C$_6$H$_5$	not isolated	5.0		0.4 (3 H, *J* = 7.0), 3.4 (q, 2 H, *J* = 7.0), 7.5 (m, 15 H)
H	CO$_2$C$_2$H$_5$	**21**[d]	C$_6$H$_5$	CO$_2$C$_2$H$_5$	C$_6$H$_5$	169–170[c]	43	DMF, 25 °C, 24 h	0.96 (t, 3 H, *J* = 7.0), 4.04 (q, 2 H, *J* = 7.0), 7.3 (m, 16 H)
		22	CO$_2$C$_2$H$_5$	C$_6$H$_5$	C$_6$H$_5$	not isolated	22		0.4 (t, 3 H, *J* = 7.0), 3.4 (q, 2 H, *J* = 7.0), 7.3 (m, 16 H)
CH$_3$	CO$_2$C$_2$H$_5$	**23**	*p*-CH$_3$C$_6$H$_4$	CO$_2$C$_2$H$_5$	C$_6$H$_5$	196–197[e]	18	DMF, 25 °C, 24 h	1.0 (t, 3 H, *J* = 7.0), 2.2 (s, 3 H), 4.1 (q, 2 H, *J* = 7.0), 7.1 (m, 15 H)
		24	CO$_2$C$_2$H$_5$	*p*-CH$_3$C$_6$H$_4$	C$_6$H$_5$	236–237[f]	7.0		0.34 (t, 3 H, *J* = 7.0), 2.28 (s, 3 H), 3.55 (q, 2 H, *J* = 7.0), 7.1 (m, 15 H)
OCH$_3$	CO$_2$C$_2$H$_5$	**25**	*p*-CH$_3$OC$_6$H$_4$	CO$_2$C$_2$H$_5$	C$_6$H$_5$	184–186[g]	17	DMF, 25 °C, 43 h	1.0 (t, 3 H, *J* = 7.0), 3.64 (s, 3 H), 4.10 (q, 2 H, *J* = 7.0), 6.63 (m, 2 H), 7.5 (m, 13 H)
		26	CO$_2$C$_2$H$_5$	*p*-CH$_3$OC$_6$H$_4$	C$_6$H$_5$	not isolated	7.2		0.4 (t, 3 H, *J* = 7.0), 3.77 (s, 3 H), 3.65 (q, 2 H, *J* = 7.0), 6.63 (m, 2 H), 7.5 (m, 13 H)
H	CO$_2$C$_2$H$_5$	**27**	C$_6$H$_5$	CO$_2$C$_2$H$_5$	*m*-FC$_6$H$_4$	201–203[h]	19	DMF, 25 °C, 10 h	1.0 (t, 3 H, *J* = 7.0), 4.11 (q, 2 H, *J* = 7.0), 7.4 (m, 15 H)
		28	CO$_2$C$_2$H$_5$	C$_6$H$_5$	*m*-FC$_6$H$_4$	not isolated	9.3		0.37 (t, 3 H, *J* = 7.0), 3.68 (q, 2 H, *J* = 7.0), 7.4 (m, 15 H)
H	CO$_2$C$_2$H$_5$	**29**	C$_6$H$_5$	CO$_2$C$_2$H$_5$	*p*-CH$_3$OC$_6$H$_4$	not isolated[i]	20	DMF, 25 °C, 24 h	0.96 (t, 3 H, *J* = 7.0), 3.61 (s, 3 H), 4.1 (q, 2 H, *J* = 7.0), 7.5 (m, 15 H)
		30	CO$_2$C$_2$H$_5$	C$_6$H$_5$	*p*-CH$_3$OC$_6$H$_4$	195–197[i]	9.1		0.38 (t, 3 H, *J* = 7.0), 3.56 (s, 3 H), 3.68 (q, 2 H, *J* = 7.0), 7.5 (m, 15 H)
H	H	**31**	C$_6$H$_5$	H	C$_6$H$_5$	229–230[j]	48	DMF, 100 °C, 24 h	6.7 (d, 1 H, *J* = 3.0), 7.2 (m, 15 H), 8.2 (d, 1 H, *J* = 6.0)
						229–230	48	DMF, −20 °C, 6 h	
Cl	H	**32**	*p*-ClC$_6$H$_4$	H	C$_6$H$_5$	235–236	44	DMF, 100 °C, 24 h	6.7 (d, 1 H, *J* = 3.0), 7.2 (m, 14 H), 8.2 (d, 1 H, *J* = 6.0)
CH$_3$	H	**33**	*p*-CH$_3$C$_6$H$_4$	H	C$_6$H$_5$	264–265	52	DMF, 100 °C, 24 h	2.2 (s, 3 H), 6.7 (d, 1 H, *J* = 3.0), 7.2 (m, 14 H), 8.3 (d, 1 H, *J* = 6.0)
OCH$_3$	H	**34**	*p*-CH$_3$OC$_6$H$_4$	H	C$_6$H$_5$	264–266	30	DMF, 100 °C, 24 h	3.7 (s, 3 H), 6.7 (m, 3 H), 7.2 (m, 12 H), 8.4 (d, 1 H, *J* = 6.0)
NO$_2$	H	**35**	*p*-O$_2$NC$_6$H$_4$	H	C$_6$H$_5$	166–168	38	DMF, 100 °C, 24 h	6.8 (d, 1 H, *J* = 3.0), 7.3 (m, 12 H), 8.0 (m, 2 H), 8.3 (d, 1 H, *J* = 6.0)
(CH$_3$)$_2$N	C$_6$H$_5$	**36**[k]	*p*-(CH$_3$)$_2$NC$_6$H$_4$	C$_6$H$_5$	C$_6$H$_5$	248–249	23	DMF, 100 °C, 24 h	2.7 (s, 6 H), 6.25 (m, 2 H), 6.4 (m, 2 H), 7.2 (m, 15 H), 8.25 (d, 1 H, *J* = 6.0)
OCH$_3$	C$_6$H$_5$	**37**	*p*-CH$_3$OC$_6$H$_4$	C$_6$H$_5$	C$_6$H$_5$	213–215[l]	18	DMF, 100 °C, 24 h	3.55 (s, 3 H), 6.4 (m, 2 H), 7.2 (m, 17 H), 8.2 (d, 1 H, *J* = 6.0)
		38	C$_6$H$_5$	*p*-CH$_3$OC$_6$H$_4$	C$_6$H$_5$	not isolated	9.0		3.75 (s, 3 H), 6.4 (m, 2 H), 7.2 (m, 17 H), 8.2 (d, 1 H, *J* = 6.0)

CH_3	C_6H_5	**39**	p-$CH_3C_6H_4$	C_6H_5	C_6H_5	228–230[m]	21	DMF, 100 °C, 24 h	2.06 (s, 3 H), 7.2 (m, 19 H), 8.25 (d, 1 H, J = 6.0)
		40	C_6H_5	p-$CH_3C_6H_4$	C_6H_5		9.0		2.26 (s, 3 H), 7.2 (m, 19 H), 8.25 (d, 1 H, J = 6.0)
H	C_6H_5	**41**	C_6H_5	C_6H_5	C_6H_5	268–270[n]	34	DMF, 100 °C, 24 h	7.2 (m, 20 H), 8.2 (d, 1 H, J = 6.0)
Cl	C_6H_5	**42**[k]	p-ClC_6H_4	C_6H_5	C_6H_5	258–259[o]	35	DMF, 100 °C, 24 h	7.2 (m, 19 H), 8.25 (d, 1 H, J = 6.0)
NO_2	C_6H_5	**43**[k]	p-$O_2NC_6H_4$	C_6H_5	C_6H_5	263–264[p]	45	DMF, 100 °C, 24 h	7.3 (m, 19 H), 8.3 (d, 1 H, J = 6.0)
1-hexene		**44**	C_4H_9	H	C_6H_5	123–124[q]	2.0	DMF, −20 °C, 6 h	0.9 (t, 3 H, J = 6.0), 1.4 (m, 4 H), 2.5 (t, 2 H, J = 7.0), 6.4 (d, 1 H, J = 3.0), 7.0 (m, 4 H), 7.4 (m, 5 H), 7.9 (d, 1 H, J = 6.0), 8.2 (m, 1 H)
							4.5	DMF, 0 °C, 6 h	
							30	DMF, 25 °C, 6 h	
							42	DMF, 25 °C, 24 h	
cyclohexene		**45**[r]				194–196[s]	0.1	DMF, −20 °C, 6 h	1.8 (m, 4 H), 2.7 (m, 4 H), 7.4 (m, 10 H), 8.2 (d, 1 H, J = 6.0)
							9.4	DMF, 25 °C, 6 h	
							37	DMF, 25 °C, 36 h	
cis-2-heptene		**46**	C_4H_9	CH_3	C_6H_5	oil[t]	0	DMF, 25 °C, 6 h	0.9 (m, 7 H), 2.3 (s, 3 H), 2.4 (m, 2 H), 7.3 (m, 11 H)
							1.5	DMF, 80 °C, 72 h	
		47	CH_3	C_4H_9	C_6H_5	oil[t]	0	DMF, 25 °C, 6 h	1.3 (m, 7 H), 2.1 (s, 3 H), 2.4 (m, 2 H), 7.3 (m, 11 H)
							0.5	DMF, 80 °C, 72 h	

[a] All pyrroles except for compounds **27–30** were prepared from the Reissert salt, 2-benzoyl-1,2-dihydroisoquinaldinitrile hydrofluoroborate. Compounds **19**, **20** and **29**, **30** were prepared from the hydrofluoroborate salts of 2-(m-fluorobenzoyl)-1,2-dihydroisoquinaldonitrile and 2-(p-anisoyl)-1,2-dihydroisoquinaldonitrile, respectively. [b] Anal. Calcd for $C_{28}H_{21}O_4N_3$: C, 72.58; H, 4.53; N, 9.08. Found: C, 72.72; H, 4.45; N, 8.89. [c] A known compound; lit.[19] mp 169–170 °C. [d] An unambigious synthesis of this compound has been previously reported in the literature.[19] [e] Anal. Calcd for $C_{29}H_{24}O_2N_2$: C, 80.53; H, 5.59; N, 6.48. Found: C, 80.48; H, 5.49; N, 6.43. [f] Anal. Calcd for $C_{29}H_{24}O_2N_2$: C, 80.53; H, 5.59; N, 6.48. Found: C, 80.15; H, 5.50; N, 6.39. [g] Anal. Calcd for $C_{29}H_{24}O_3N_2$: C, 77.66; H, 5.39; N, 6.25. Found: C, 77.45; H, 5.10; N, 6.03. [h] Anal. Calcd for $C_{28}H_{21}FN_2O_2$: C, 77.05; H, 4.85; F, 4.35; N, 6.42. Found: C, 77.09; H, 5.05; F, 4.37; N, 6.51. [i] Anal. Calcd for $C_{29}H_{24}N_2O_3$ (mixture): C, 77.66; H, 5.39; N, 6.25. Found: C, 77.48; H, 5.24; N, 6.35. [j] A known compound; lit.[17] mp 226–228 °C. [k] Trace amounts of the other isomer were presumably formed. [l] A known compound; lit.[15] mp 212–213 °C. [m] Melting point of mixture. Anal. Calcd for $C_{32}H_{24}N_2$ (mixture): C, 88.04; H, 5.54; N, 6.42. Found: C, 88.53; H, 5.92; N, 5.99. [n] A known compound; lit.[12] mp 263–264 °C. [o] Anal. Calcd for $C_{31}H_{21}N_2Cl$: C, 81.48; H, 4.63; N, 6.13; Cl, 7.76. Found: C, 81.62; H, 5.14; N, 5.61; Cl, 7.87. [p] Anal. Calcd for $C_{31}H_{21}N_3O_2$: C, 79.64; H, 4.53. Found: C, 79.67; H, 4.52. [q] Anal. Calcd for $C_{23}H_{22}N_2$: C, 84.63; H, 6.79; N, 8.58. Found: C, 84.60; H, 6.73; N, 8.58. [r] See structure **45** in the main text. [s] Anal. Calcd for $C_{23}H_{20}N_2$: C, 85.15; H, 6.21; N, 8.63. Found: C, 85.07; H, 6.22; N, 8.67. [t] All attempts to separate the mixture of the two isomers proved unsuccessful.

paring the integrations of the methyl protons of the *p*-methylstyrene product with the aromatic region. The results of the competition runs with *p*-methoxystyrene were verified by comparison with the integration of the methoxy protons. Separation of the peaks corresponding to the N–H protons of the pyrroles was observed only in the competition runs of *p*-methylstyrene vs. *p*-nitrostyrene. Comparison of their relative integrations further confirmed the relative rates of reaction. For minimization of experimental error, all experiments were carried out in duplicate. The relative rates of reaction of the styrenes (Table III) were correlated by use of the Hammett equation and gave a ρ value of +0.74.

(E) Kinetics Studies. Cycloaddition Reactions of 2-Aroyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborates (5) with Substituted Ethyl Cinnamates (6). Rate constants (k_2) determined for reactions of the Reissert salts with substituted ethyl cinnamates are reported in Table I. For each study, a solution of 0.0131 mol of the Reissert salt and 30.0 mL of purified DMF[24] in a 250-mL, three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a stopper was allowed to equilibrate in a constant-temperature bath at 32.7 ± 0.1 °C. To this solution was added 0.0131 mol of a freshly distilled or recrystallized substituted ethyl cinnamate (**6**). Zero time was defined as the instant of complete mixing of the reagents. A 2.00-mL aliquot of the reaction mixture was removed at certain time intervals, and the reaction was quenched by adding the aliquot to 20 mL of saturated sodium bicarbonate solution. The mixture was extracted thoroughly with 60 mL of benzene, and the benzene solution was concentrated to dryness. The residue was dissolved in a minimum amount of spectrograde chloroform and transferred to a precalibrated vial. The flask was washed with small amounts of the same solvent, and the combined chloroform solution was adjusted to exactly 2.0 mL. The IR spectra were taken on a Beckmann IR-10 spectrophotometer, the disappearance of the absorption at 612 cm^{-1} (or 585 cm^{-1} in the case of 2-(*p*-methoxybenzoyl)-1,2-dihydroisoquinaldonitrile) being observed. This absorption peak is attributable to the nonaromatic cis C–C double bond of the Reissert compound, which is produced quantitatively when the reaction is quenched. Calibration curves for the Reissert salts were constructed by taking IR spectra of their solutions of known concentration in spectrograde chloroform. The plots were found to fit Beer's law. From the IR spectra of the material derived from the aliquots and the calibration curves, the concentrations of unchanged Reissert compound or Reissert salt at each time could be determined. Plots of $1/c$ vs. t were then constructed, and all were found to be linear. The second-order rate constants were obtained directly by calculating the slope of each plot. The rates of reaction of the substituted cinnamates with 2-benzoyl-1,2-dihydroisoquinaldonitrile were correlated by use of the Hammett equation and gave a ρ value of +1.24.

The ethyl group of the ethoxycarbonyl group of the compounds derived from the ethyl cinnamates appears to be strongly shielded, presumably by the isoquinoline ring, when attached at the position designated by R_1 (Table VI), as compared to the case of the isomers having the ethoxycarbonyl group at R_2. The shielding effect is diagnostic of the six pairs of isomers described; presumably the isoquinoline and pyrrole rings are not coplanar.

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Registry No. 4 (R = C_6H_5), 68001-26-3; **5** (Y = *m*-F), 76583-40-9; **5** (Y = *p*-OMe), 41745-69-1; **6** (X = NO_2), 24393-61-1; **6** (X = H), 4192-77-2; **6** (X = Me), 24393-49-5; **6** (X = OMe), 24393-56-4; **10** (X = NMe_2), 76583-62-5; **10** (X = Cl), 76583-63-6; **10** (X = NO_2), 51039-60-2; **19**, 53778-27-1; **20**, 76583-41-0; **21**, 53778-22-6; **22**, 76583-42-1; **23**, 76583-43-2; **24**, 76583-44-3; **25**, 76583-45-4; **26**, 76583-46-5; **27**, 76583-47-6; **28**, 76583-48-7; **29**, 76583-49-8; **30**, 76583-50-1; **31**, 53778-23-7; **32**, 76583-51-2; **33**, 76583-52-3; **34**, 76599-26-3; **35**, 76583-53-4; **36**, 76583-54-5; **37**, 27123-16-6; **38**, 28506-35-6; **39**, 76583-55-6; **40**, 76583-56-7; **41**, 10425-52-2; **42**, 76583-57-8; **43**, 51039-61-3; **44**, 76583-58-9; **45**, 76583-59-0; **46**, 76583-60-3; **47**, 76583-61-4; 2-(*m*-fluorobenzoyl)-1,2-dihydroisoquinaldonitrile, 76583-64-7; 2-(*p*-anisoyl)-1,2-dihydroisoquinaldonitrile, 58021-73-1; $C_6H_5CH{=}CH_2$, 100-42-5; *p*-$ClC_6H_4CH{=}CH_2$, 1073-67-2; *p*-$MeC_6H_4CH{=}CH_2$, 622-97-9; *p*-$OMeC_6H_4CH{=}CH_2$, 637-69-4; *p*-$NO_2C_6H_4CH{=}CH_2$, 100-13-0; *trans-p*-$NMe_2C_6H_4CH{=}CHC6H_5$, 838-95-9; *trans-p*-$OMeC_6H_4CH{=}CHC_6H_5$, 1694-19-5; *trans-p*-$MeC_6H_4CH{=}CHC_6H_5$, 1860-17-9; *trans*-$C_6H_5CH{=}CHC_6H_5$, 103-30-0; *trans-p*-$ClC_6H_4CH{=}CHC_6H_5$, 1657-50-7; *trans-p*-$NO_2C_6H_4CH{=}CHC_6H_5$, 1694-20-8; 1-hexene, 592-41-6; cyclohexene, 110-83-8; *cis*-2-heptene, 6443-92-1.