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The Reaction of *N*-Aryl-*C*-ethoxycarbonylnitrilimine with Olefins[1]

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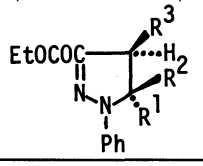
C-Ethoxycarbonylnitrilimines treated with monosubstituted olefins predominantly gave 5-substituted 3-ethoxycarbonyl-2-pyrazolines. From the analysis of the relative rate and regioselectivity of a variety of monosubstituted olefins for the cycloaddition, the nitrilimine is shown to have reactivity and regioselectivity similar to the throughly studied diphenylnitrilimine. The cycloaddition regioselectivity is discussed in terms of frontier orbital energies and coefficients.

Nitrilimines have been widely investigated and are one of the most versatile 1,3-dipoles for cycloaddition. *C*-Ethoxycarbonylnitrilimines especially have led to the synthesis of functional heterocyclic compounds. The reactivity of 1,3-dipolar cycloaddition reactions has been explained by frontier molecular orbital (FMO) theory,[2] but only a qualitative prediction has been made for the reactivity of nitrilimines. Recently, diphenylnitrilimine was identified at 85 K.[3] But the structural data of the nitrilimine can not be applied to the prediction of reactivity of the nitrilimine at ambient temperature. Some 1,3-dipoles react with monosubstituted electron-rich olefins to form products predicted by dipole-LUMO control. However for conjugated and electron-deficient dipolarophiles the regiochemistry of the reaction depends on which frontier orbital interaction (dipole-HOMO/dipolarophile-LUMO or dipole-LUMO/dipolarophile-HOMO) is dominant.[2] The reaction of diphenylnitrilimine with monosubstituted olefins gives predominantly 5-substituted 2-pyrazolines[4] and the orientation phenomena can be explained more or less satisfactorily by electronic effects alone. Dipole-LUMO/dipolarophile-HOMO interaction only controls the reaction of *N*-phenylsulfonylnitrilimine.[5] While the preparation and reaction of *C*-ethoxycarbonylnitrilimines have been the subject of intensive study,[6,7] a systematic investigation of the reactivity has not been carried out. Recently, 4-substituted 2-pyrazolines were claimed to be the exclusive products of the reaction of *C*-ethoxycarbonyl-*N*-arylnitrilimines with acrylic acid derivatives,[7] although the structure was assigned tentatively on the

TABLE 1. YIELDS, MELTING POINTS, AND ANALYTICAL DATA OF **2**



2

	R^1	R^2	R^3	Yield %	Mp θ_m/°C	Found(Calcd) (%) C	H	N
2a	Ph	H	H	85[d]	86—87	73.62 (73.45	6.15 6.16	9.55 9.52)
2b	CO_2Me	H	H	80[d]	83—84	60.71 (60.86	5.79 5.84	10.02 10.14)
2c	CN	H	H	70[d]	98—100	64.45 (64.18	5.41 5.39	17.38 17.28)
2d	$CONH_2$	H	H	81[d]	212—213	59.70 (59.76	5.77 5.79	16.05 16.08)
2e	*n*-Bu	H	H	80[e]				
2f	OBu-*n*	H	H	100[e]				
2g	CO_2Et	H	CH_3	100[e]				
2h	CO_2Me	CH_3	H	78[d]	100—101	62.25 (62.05	6.27 6.25	9.65 9.65)
2i[a]	H	$-C_5H_8-$		100[d]	82—83	71.85 (71.80	7.06 7.09	9.85 9.85)
2j	CO_2Me	H	CO_2Me	100[d]	78—80	57.23 (57.48	5.48 5.43	8.39 8.38)
2k[b]	H	$-C_4H_8-$		85[e]				
2m[c]	COPh	H	Ph	43[c]	133—138[c]	74.64 (74.59	5.73 5.74	7.22 7.25)
2n[c]	Ph	H	COPh	29[c]				

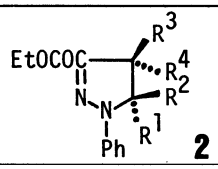
a) Cycloadduct of norbornene. b) Cycloadduct of cyclohexene. c) The mixture of **2m** and **2n** was obtained from the reaction with chalcone, and the ratio was determined by NMR. d) Isolated yields. e) Estimated from NMR.

basis of FMO theory only. We have investigated the reactivity and regioselectivity of *C*-ethoxycarbonyl-*N*-arylnitrilimines toward olefins.

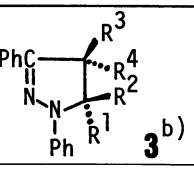
Results and Discussion

Cycloadducts (**2**) were obtained when the reaction of olefins with ethyl chloroglyoxylate arylhydrazones (**1**) was carried out in the presence of triethylamine (Table 1). NMR analysis of the reaction mixture showed that the cycloadducts were formed quantitatively but an attempt to isolate pure material from liquid product (**2i**) by distillation failed because of decomposition to 3-ethoxycarbonyl-1-phenylpyrazole (**4**), which was also obtained in high yield by distillation of the reaction mixture of **1** with vinyl acetate. The structure of the cycloadducts was identified on the basis of elemental analysis and of their characteristic IR and NMR spectra. Both electron-rich and electron-deficient monosubstituted olefins gave exclusively one of two possible isomers, 5-substituted 2-pyrazolines. A distinction between the two isomers was made on the basis of the chemical shift of the methylene and methine hydrogens on the pyrazoline ring in the NMR spectra (Table 2). The three hydrogens show ABX or A_2X patterns depending on the substituent. Methylene chemical shifts at both 4- and 5-positions would be expected to be approximately same and in our cases the appearance of the methylene protones at δ 2.6—3.7 is compatible with both assignment. The methine chemical shift at the 5-position would be expected to appear at lower field than that at the 4-position,[8] although the chemical shift data for CH are much less abundant and less reliable than those for $-CH_2-$. The methine chemical shift at δ 4.0—5.8 was too low to be assigned to CH at the 4-position. Several attempts to prepare an authentic 4-substituted 2-pyrazoline failed, and therefore, we compared the chemical shifts with those of the thoroughly studied diphnylnitrilimine cycloadducts(**3**)[9a] (Table 2). Both substituents, phenyl and ethoxycarbonyl at 3-position, would have roughly the same effects on the chemical shift of methylene protones at the 4-position. Between the cycloadducts (**2** and **3**) having the same substituent at the 5-position each of methine and metylene protons shows comparable chemical shifts. Tewari *et al.*[7a] and Padwa *et al.*[7b] assigned 4-substituted 2-pyrazoline structures to the reaction products from *C*-ethoxycarbonyl-*N*-arylnitrilimines and acrylamide or methyl acrylate, respectively, on the basis of orbital interaction as discussed later. We confirmed these reactions but the chemical shifts of the products showed comparable δ values to ours. Thus, it seems reasonable to assume that all *C*-ethocycarbonylnitrilimines prepared so far give 5-substituted 2-pyrazolines almost exclusively, when reacted with monosubstituted olefins.

Table 2. NMR spectral data of **2** and **3**[a]



2



3[b]

	R^2(5-H)	R^3(4-H)	R^4(4-H)	R^2(5-H)	R^3(4-H)	R^4(4-H)
a	5.33(dd) *J*=8 and 13 Hz,	3.67(dd) *J*=13 and 18 Hz,	2.95(dd) *J*=8 and 18 Hz,	5.19(dd) *J*=8 and 12.1 Hz,	3.75(dd) *J*=12.1 and 16 Hz,	3.06(dd) *J*=8 and 16 Hz
b	4.90(dd) *J*=8 and 11 Hz,	3.20(dd) *J*=8 and 18 Hz,	3.57(dd) *J*=11 and 18 Hz,	4.62(dd) *J*=8 and 11 Hz,	3.20(dd) *J*=11 and 17 Hz,	3.38(dd) *J*=8 and 17 Hz
c	5.04(t) *J*=9 Hz	3.50(d) *J*=9 Hz		4.88(t)	3.55(d)	
d	4.90(dd) *J*=8 and 13 Hz,	2.97(dd) *J*=8 and 18 Hz,	3.54(dd) *J*=13 and 18 Hz	----------		
e	4.2—4.5(m)	3.25(dd) *J*=10 and 18 Hz,	2.80(dd) *J*=7 and 18 Hz,	4.02(m)	3.25(dd) *J*=11 and 17 Hz,	2.83(dd) *J*=6 and 17 Hz
f	5.73(t) *J*=6 Hz,	3.07(d) *J*=6 Hz		----------		
g	4.47(d) *J*=5 Hz,	—	3.60(dq) *J*=5 and 7 Hz,	4.43(d) *J*=4 Hz,	—	3.73(m)
h	—	3.10(d) *J*=18 Hz,	3.58(d) *J*=18 Hz,	—	3.15(d) *J*=17 Hz,	3.57(d) *J*=17 Hz
i	4.08(d) *J*=10 Hz,	3.28(d) *J*=10 Hz,	—	4.02(d) *J*=10 Hz,	3.44(d) *J*=10 Hz,	—
j	5.15(d) *J*=6 Hz,	—	4.37(d) *J*=6 Hz,	5.17(d) *J*=5 Hz,	—	4.57(d) *J*=5 Hz
k	4.0—4.5(m)	2.7—3.6(m)	—	----------		
m	5.77(d) *J*=5 Hz,	—	4.43(d) *J*=5 Hz,	5.61(d) *J*=5 Hz,	—	4.61(d) *J*=5 Hz
n	5.47(d) *J*=7 Hz,	—	5.07(d) *J*=7 Hz,	----------		

a) **2d** was dissolved in DMSO-d_6, the others were dissolved in $CDCl_3$. b) Data were cited from Ref. 9a and 11.

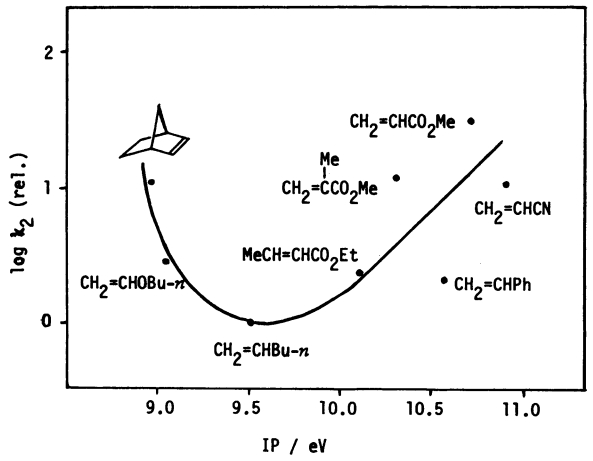


Fig. 1. The relative reaction rates and the ionic potentials of the dipolarophiles.

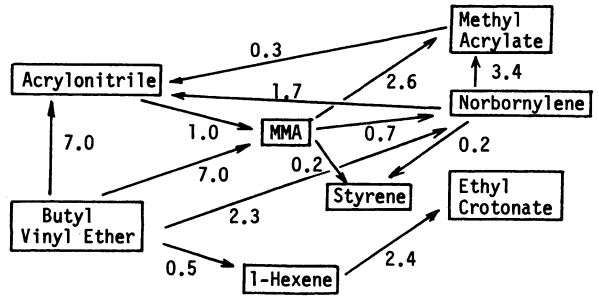


Fig. 2. The relative reaction rates of the diporaro-philes.
The numbers show relative reaction rates, x, where $x=k_B/k_A$ in the presence of both dipolarophiles, A and B. (B is shown after the arrow.)

In order to obtain additional criteria for the reactivity of the nitrilimine, competitive reactions of **1** were carried out between a variety of pairs of dipolarophiles (Fig. 2.). Relative rates in reference to 1-hexene are shown in Fig 1. These results clearly indicate that *C*-ethoxycarbonylnitrilimine is similar in reactivity to diphenylnitrilimine[9b] except for a lower reactivity toward electron-poor dipolaropiles.

The interpretation of the reactivity and regioselectivity of cycloadditions of the nitrilimine with electron-rich or conjugated olefins is fully in agreement with the prediction[2] that dipole-LUMO/dipolarophile-HOMO interaction is important and 5-substituted 2-pyrazolines are favored. On the other hand, it should be expected that the reaction of electron-deficient dipolarophiles and nitrilimines having relatively high HOMO energy is controlled by dipole-HOMO/dipolarophile-LUMO interaction. It is erroneously accepted that the coefficient of the nitrogen atom in HOMO of diphenylnitrilimine is much larger than that of the carbon atom. Consequently, the 4-substituted 2-pyrazolines are favored or the predominant formation of 5-substituted 2-pyrazolines with electron-deficent dipolarophiles can be only explained by an energetically unfavorable dipole-LUMO/dipolarophile-HOMO interaction [see interaction (a) in Fig. 3] based on the erroneous assumption.[2a] Recently, Houk and Caramella on the basis of *ab initio* molecular orbital calculations argued that in the non-planar most stable conformation of H-C≡$\overset{+}{N}$-$\bar{N}$-H the biggest HOMO coefficient is to be found on the carbon atom[10] and this is also the case in diphenylnitrilimine.[11] Therefore the formation of 5-substituted 2-pyrazolines can be explained satisfactorily on the basis of dipole-HOMO control [see interaction (c) in Fig. 3] by assuming that the coefficient of carbon atom in HOMO of diphenyl- or *C*-ethoxycarbonyl-*N*-phenylnitrilimine is much larger than that of nitrogen atom.

Experimintal

Measurements. All the melting and boiling points are uncorrected. The IR spectra were determined on a Hitachi 215 Infrared Spectrophotometer. The ^{1}H NMR spectra were measured on a Varian T-60A instrument with TMS as an internal standard.

Materials. Ethyl chloroglyoxalate phenylhydrazone (**1**)[12] was prepared according to the method described in the literature. All the olefins are commercially available and

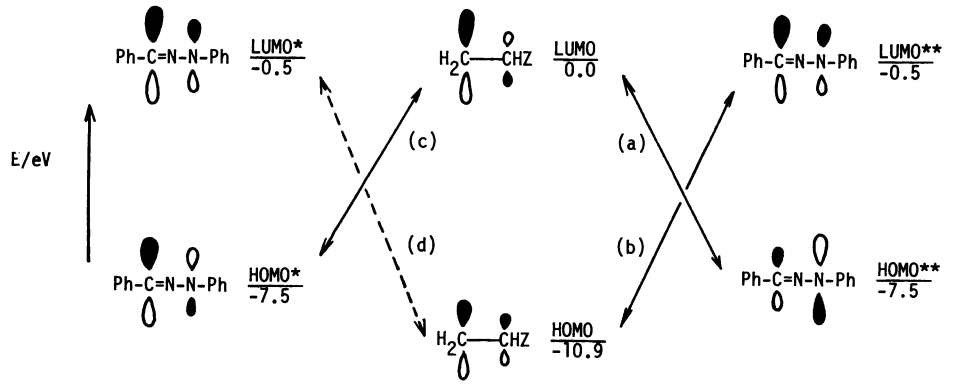


Fig. 3. Frontier orbital interactions (a—d) of diphenylnitrilimine and electron-deficient olefins.
* Magnitude of the coefficients is estimated from the calculation based on *ab initio* molecular orbital method.[10,11]
** Magnitude of the coefficients is estimated from the calculation based on CNDO/2 molecular orbital method.[2a]

were used after fractional distillation under nitrogen.

Reaction of 1 with Olefins. General Method: To a stirred chloroform (100 ml) solution of triethylamine (2.7 g, 26.4 mmol) and olefin (40 ml), was added a chloroform (20 ml) solution of ethyl chloroglyoxalate phenylhydrazone (3.0 g, 13.2 mml) at room temperature. After refluxing the chloroform solution for 2 h, the reaction mixture was cooled, washed with water several times. The chloroform solution was dried over sodium sulfate and the solvent and an excess amount of olefin were evaporated in a rotary evaporator at up to 60 °C *in vacuo*, giving crystals (**2a—d**, **2h—j**, **2m**, and **2n**), which were recrystallized from ethanol. Analysis of the residue by NMR after the evaporation gave aproximate yields of the other oily products as shown in Table 1. Distillation of the reaction mixture of **1** and butyl vinyl ether *in vacuo* gave 3-ethoxycarbonyl-1-phenylpyrazole (**4**) quantitatively; bp 180—185 °C/2 mmHg (1 mmHg≈133.322 Pa). NMR ($CDCl_3$) δ=1.33 (t, 3H, J=7 Hz), 4.37 (q, 2H, J=7 Hz), 6.95 (d, 1H, J=2 Hz), 7.0—7.85 (m, 5H), and 8.0 (d, 1H, J=2Hz).

Relative Reaction Rate of Dipolarophiles in Cycloaddition of C-Ethoxycarbonyl-N-phenylnitrilimine. This measurement was carried out according to the method described in the literature.[9b] To a refluxing chloroform solution (100 ml) of ten molar equivalents (0.13 mol) of two kind of dipolarophile and triethylamine (0.13 mol), was added dropwise a chloroform solution (20 ml) of ethyl chloroglyoxalate phenylhydrazone (3.0 g, 13 mmol) over a period of 1 h. After cooled to room temperature, the mixture was washed with water several times, dried (Na_2SO_4) and the solvent and the excess of the dipolarophiles was evaporated *in vacuo* at up to 60 °C. The residue was analysed by NMR in deuteriochloroform and the ratio of the competitive reaction products between dipolarophiles were estimated from the integration of each characteristic peaks. The results of the measurements are shown in Fig. 2.

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