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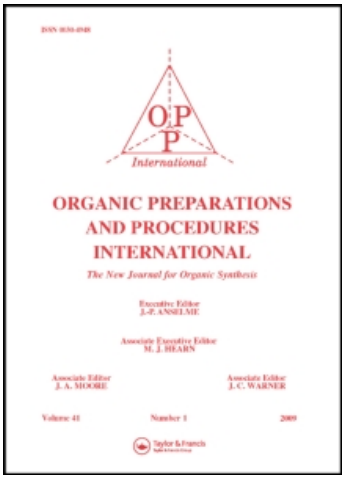

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SYNTHESIS OF PYRAZOLES AND 2-PYRAZOLINES FROM C-PHENYLAMINOCARBONYL-N-ARYLFORMOHYDRAZIDOYL CHLORIDES

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SYNTHESIS OF PYRAZOLES AND 2-PYRAZOLINES FROM C-PHENYLAMINOCARBONYL-N-ARYLFORMOHYDRAZIDOYL CHLORIDES

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Although the synthesis and reactions of C-phenylaminocarbonyl-N-aryl-formohydrazidoyl chlorides 1 have been the subject of several reports,[1-3] the cycloaddition reactions of 1 has received little attention. We now report the results of our study of the cycloaddition of 1 to α,β-unsaturated ketones and α,β-disubstituted acrylonitriles. The cycloaddition regioselectivity is discussed in terms of frontier energies and coefficients. Treatment of C-phenylamino-carbonyl-N-arylnitrilimines 2a-e, generated in situ by treatment of C-phenyl-aminocarbonyl-N-arylformohydrazidoyl chlorides 1a-e with triethylamine, with α,β-unsaturated ketones 3-6 was carried out in refluxing benzene. The results of these reactions are summarized in Table 1. These results show that 1 reacts with α,β-unsaturated ketones to give as a rule only 1,4-diaryl-3-phenyl-aminocarbonyl-5-aroyl-2-pyrazoline derivatives 7-10 (Scheme 1); in no case was the other regioisomer 11 detected. This regiochemical result was found to be independent of the nature of the solvent. Thus, when the reaction of 1a and 3a was carried out in chloroform, acetonitrile, 1,2-dichloroethane, or ethyl acetate, 1,4-diphenyl-3-phenylaminocarbonyl-5-benzoyl-2-pyrazoline (7a) was the exclusive product. This result is similar to that reported for the reaction of N-phenyl-C-phenylformohydrazidoyl chloride with benzylideneaceto-phenone (3a)[4] and in contrast with the solvent polarity effect found for the reaction of nitrile oxide with 3a.[5] The structures of the cycloadducts 7-10 were assigned on the basis of elemental analysis and spectroscopic data (IR

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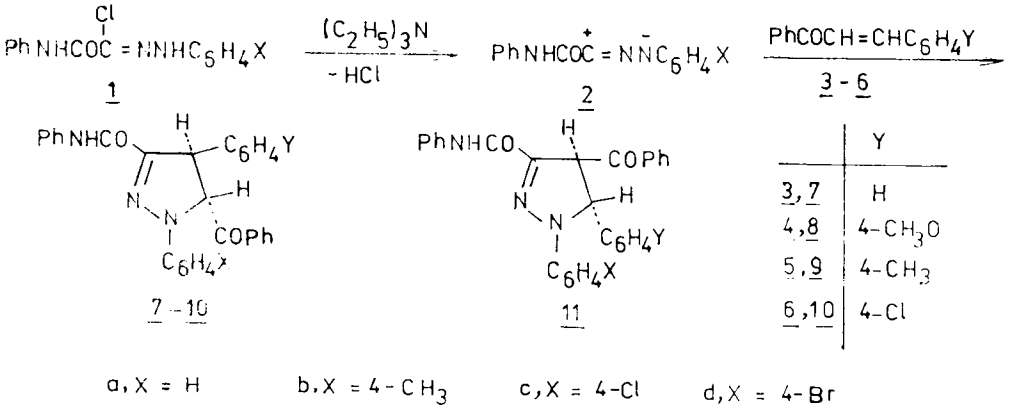
and ^{1}H-NMR). The ^{1}H-NMR spectra of 7-10 were characterized, in each case, by the presence of two doublets (J = 6Hz) near δ 4.60-4.70 and 5.70-5.80 ppm due to 4-H and 5-H, respectively.[6] On the basis of the coupling constant value, the cycloadducts 7-10 were assigned a trans configuration.[7]



Scheme 1

Treatment of 1a with benzalmalononitrile 12 in boiling chloroform in presence of triethylamine yielded 1,4-diphenyl-3-phenylcarbamoyl-5-cyanopyrazole 13. Neither the 2-pyrazoline 14 nor the triazole 15 were detected. This suggests that the 5,5-dicyano-2-pyrazoline 16 is easily aromatized by thermal elimination of hydrogen cyanide (Scheme 2). This thermal elimination of hydrogen cyanide from 16 to give 13 is similar to thermal elimination of hydrazoic acid from 1,3,4-triphenyl-5-benzoyl-5-azido-2-pyrazoline.[8] The structure of the product 13 was established by elemental analysis, ^{1}H-NMR and IR spectra (Table 1). The regiochemistry of 13 was confirmed by comparison of the properties of 13 with those of the pertinent regioisomer, 1,5-diphenyl-3-phenylaminocarbonyl-4-cyanopyrazole 17. The latter was prepared by the reaction of 1 with the sodium salt of phenacyl cyanide in ethanol at room temperature (Scheme 3).

The reflux of 1a with α,β-disubstituted acrylonitriles 18-20 in chloroform yielded only the 2-pyrazoline derivatives 21-23 respectively (Scheme 3). The

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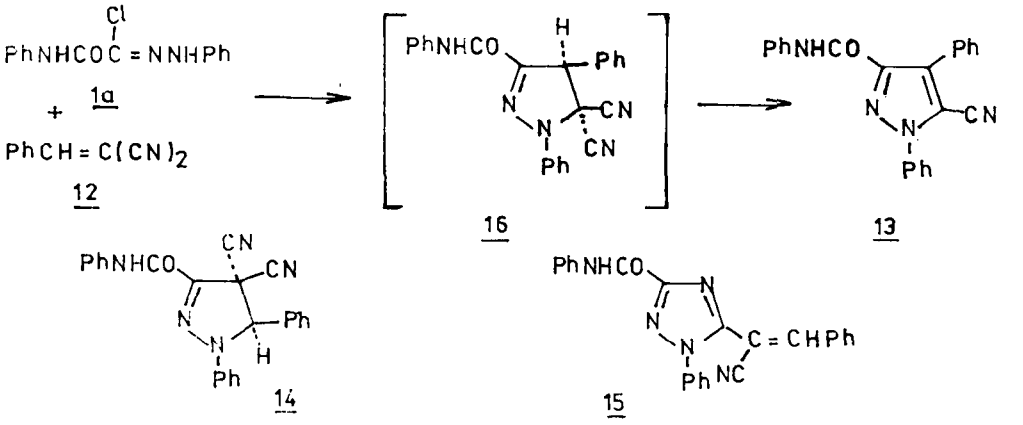
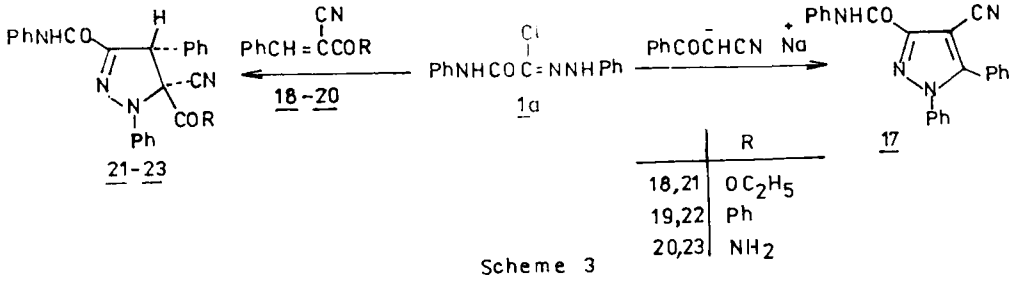


Scheme 2

assigned 5,5-disubstituted structures 21-23 were supported by analytical and spectral (IR, ^{1}H-NMR) data. For example, in the IR spectra of 21-23 the nitrile absorption was absent or very weak, if present, as in the case of aliphatic nitriles activated by a nitrogen or an oxygen atom in the α-position.[9] In ^{1}H-NMR spectra, the pyrazolines 21-23 had, in each case, characteristic singlet at δ5.2 ppm (Table 1).



Scheme 3

The foregoing results indicate that the regioselectivity in the reaction of 2 with various dipolarophiles examined is similar to that of diphenylnitrilimine.[10] Thus by analogy to the latter dipole, the cycloaddition of 2 to electron-deficient dipolarophiles such as benzalacetophenones and α,β-disubstituted acrylonitriles is controlled by HOMO (dipole)-LUMO (dipolarophile) interaction.[5] On the other hand, the reaction of 1 with electron-rich dipolarophile such as

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phenacyl cyanide is controlled by LUMO (dipole)-HOMO (dipolarophile) interaction.

EXPERIMENTAL SECTION

Melting points were determined on a Bockmonoscop apparatus (hot stage type) and are uncorrected. Infrared spectra were recorded on Zeiss infrared spectrophotometer model IMT6. ^{1}H-NMR spectra were measured in DMSO with Varian T60-A spectrometer; chemical shifts are in ppm from internal tetramethylsilane. N-Aryl-C-phenylaminocarbonylformohydrazidoyl chlorides 2a-d were prepared according to a literature method.[1] Benzylideneacetophenone 3 was obtained from Merck, and the remaining substituted benzylideneacetophenones 4-6 were prepared by condensation of the appropriate aromatic aldehyde with acetophenone following a known procedure.[11]

1,4-Diaryl-3-phenylaminocarbonyl-5-aroyl-2-pyrazolines (7-10). General Procedure.- Triethylamine (0.7 ml, 5 mmoles) was added to a stirred solution of the appropriate hydrazidoyl halide 2 (5 mmoles) and the α,β-unsaturated ketones (5 mmoles) in benzene (40 ml) at room temperature. The mixture was refluxed till the disappearance of the chloride 2 or the enone as indicated by tlc analysis (20-30 h). The precipitated triethylamine hydrochloride was collected and the filtrate was evaporated. The solid residue left was collected and crystallized from acetic acid. The cycloadducts 7-10 formed together with their physical constants are given in Table 1.

When the reaction of 1a with 3a was repeated in chloroform, 1,2-dichloroethane, acetonitrile, or ethyl acetate, 1,4-diphenyl-3-phenylaminocarbonyl-5-benzoyl-2-pyrazoline (7a) was the exclusive cycloadduct isolated.

1,4-Diphenyl-3-phenylaminocarbonyl-5-cyanopyrazole (13).- To a solution of C-phenylaminocarbonyl-N-phenylformohydrazidoyl chloride 1a (1.36 gm, 5.0 mmoles) and benzalmalononitrile 12 (0.77 gm, 5.0 mmoles) in chloroform (40 ml) was added dropwise triethylamine (0.7 ml, 5 mmoles) while stirring at room temperature. The mixture was then refluxed for 10-12 h and cooled. The reaction mixture was washed with water and the organic layer was collected and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was triturated with little methanol

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where it solidified. The crude product was collected and crystallized from acetic acid (Table 1).

1,5-Diphenyl-3-phenylaminocarbonyl-4-cyanopyrazole (17).- To an ethanolic sodium ethoxide solution (prepared from sodium metal (0.1 g, 0.005 g atom) and absolute ethanol (20 ml) was added phenacyl cyanide (0.72 gm, 5 mmoles) with stirring. To the resulting solution, the hydrazidoyl chloride 1a (1.36 gm, 5 mmoles) was added at room temperature. The mixture was stirred for 24 h during which the hydrazidoyl chloride 1a dissolved and the crude product precipitated. The latter was collected, washed with water, dried and crystallized from acetic acid (Table 1).

1,4-Diphenyl-3-phenylaminocarbonyl-5-cyano-5-R-2-pyrazolines (21-23). General Procedure.- To a stirred solution of C-phenylaminocarbonyl-N-phenylformohydrazidoyl chloride 1a (1.36 gm, 5 mmoles) and the appropriate dipolarophiles 18-20 (5 mmoles) in chloroform (40 ml) was added triethylamine (0.7 ml, 5 mmoles) at room temperature. The reaction mixture was refluxed for 15 h, then cooled. Work up of the reaction mixture as in the above procedure afforded the 2-pyrazoline derivatives 21-23 (Table 1).

Table 1. Compounds 7-10, 13, 17, 21-23

Comp.	mp. (°C)	Yield[a] (%)	NMR ($CDCl_3$) δ ppm	Analysis % Calcd (Found) C	H	N
7a	204	75	7.0-8.5 (m, 21H), 5.8 (d, 1H), 4.7 (d, 1H).	78.18 (78.20)	5.20 (5.25)	9.43 (9.31)
7b	220	80	7.0-8.5 (m, 20H), 5.8 (d, 1H), 4.6 (d, 1H), 2.5 (s, 3H).	78.41 (78.51)	5.48 (5.46)	9.14 (9.22)
7c	222	71	6.9-8.5 (m, 20H), 5.8 (d, 1H), 4.6 (d, 1H).	74.75 (74.33)	4.75 (4.82)	6.01 (6.12)
7d	205	73	6.9-8.5 (m, 20H), 5.8 (d, 1H), 4.6 (d, 1H).	66.45 (66.23)	4.23 (4.11)	8.01 (8.31)
8a	224	82	6.9-8.5 (m, 20H), 5.8 (d, 1H), 4.6 (d, 1H), 3.7 (s, 3H).	75.77 (75.21)	5.30 (5.22)	8.84 (8.62)
8b	252	74	6.9-8.5 (m, 19H), 5.8 (d, 1H), 4.6 (d, 1H), 3.8 (s, 3H), 2.5 (s, 3H)	76.05 (76.31)	5.56 (5.73)	8.58 (8.61)
8c	225	85	7.0-8.5 (m, 19H), 5.7 (d, 1H), 4.6 (d, 1H), 3.8 (s, 3H).	70.65 (70.46)	4.74 (4.61)	8.24 (8.52)

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Comp.	mp. (°C)	Yield[a] (%)	NMR ($CDCl_3$) δ ppm	Analysis % Calcd (Found) C	H	N
8d	222	83	6.8-8.5 (m, 19H), 5.8 (d, 1H), 4.6 (d, 1H), 3.7 (s, 3H).	64.99 (64.72)	4.36 (4.22)	7.58 (7.41)
9a	212	71	7.0-8.5 (m, 20H), 5.8 (d, 1H), 4.6 (d, 1H), 2.4 (s, 3H).	78.41 (78.22)	5.48 (5.52)	8.14 (9.11)
9b	237	69	7.0.8.5 (m, 19H), 5.8 (d, 1H), 4.6 (d, 1H), 2.5 (s, 3H), 2.6 (s,3H)	78.62 (78.51)	5.75 (5.61)	8.87 (8.61)
9c	250	70	6.9-8.5 (m, 19H), 5.8 (d, 1H), 4.6 (d, 1H), 2.4 (s, 3H).	72.94 (72.76)	4.90 (4.82)	8.51 (8.42)
9d	237	73	6.9-8.5 (m, 19H), 5.8 (d, 1H), 4.6 (d, 1H), 2.4 (s, 3H).	66.92 (66.81)	4.49 (4.31)	7.80 (7.92)
10a	235	72	7.0-8.5 (m, 20H), 5.8 (d, 1H), 4.6 (d, 1H).	72.57 (72.32)	4.62 (4.52)	8.75 (8.66)
10b	230	80	7.0-8.5 (m, 19H), 5.8 (d, 1H), 4.6 (d, 1H), 2.5 (s, 3H).	72.94 (72.76)	4.90 (4.81)	8.51 (8.40)
10c	228	70	7.0-8.5 (m, 19H), 5.8 (d, 1H), 4.6 (d, 1H).	67.76 (67.66)	4.11 (4.01)	8.17 (8.27)
10d	225	73	6.9-8.5 (m, 19H), 5.7 (d, 1H), 4.7 (d, 1H).	62.33 (62.41)	3.79 (3.61)	7.52 (7.61)
13	188	65	7.0-8.5 (m, Ar-H)	76.87 (76.62)	3.09 (3.22)	15.60 (15.72)
17	197	70	7.1-8.5 (m, Ar-H)	76.82 (76.81)	3.09 (3.11)	15.60 (15.71)
22	205	71	7.0-8.4 (m,21H), 5.2 (s, 1H).	76.58 (76.46)	4.71 (4.61)	11.91 (11.87)
23	252	65	7.0-8.4 (m, 21H), 6.3 (s, 2H), 5.1 (s, 1H).	70.40 (70.62)	4.68 (4.70)	17.10 (17.33)

(a) Yield of isolated pure product; all compounds were crystallized from acetic acid except compounds 21-23 were crystallized from ethanol

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