1,3-Dipolar Cycloaddition of Four Hydrazonoyl Chlorides to β-Diketones and α,β-Unsaturated Ketones

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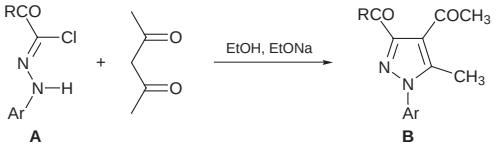
The 1,3-dipolar cycloaddition of four hydrazonoyl chloride derivatives with the sodium salt of unsymmetrical β-diketones (benzoylacetone) offers a versatile method for the regioselective synthesis of 2*H*-pyrazoles in a similar fashion to the cycloaddition of the nitrilimides with α,β-unsaturated ketones and esters; the structures of the prepared isomeric pyrazole and pyrazoline derivatives are established by spectroscopic and chemical methods.

In a recent paper,[1] we reported the cycloaddition of hydrazonoyl chlorides **3a**–**c** to benzylideneacetone, chalcones, symmetrical and unsymmetrical β-diketones and ascertained the regiostructures of the resulting pyrazole derivatives. In continuation of such study, we report herein the 1,3-dipolar cycloaddition of several hydrazonoyl chlorides **1a**–**c**, **3a**–**d**, **5a**–**d** and **13** with acetylacetone and benzoylacetone (Schemes 1 and 2). The aim of the present work was: (i) to synthesize and devise a simple method for distinguishing between the two regioisomeric pyrazoles, *viz*., 4-acetyl-5-phenyl- and 4-benzoyl-5-methylpyrazole derivatives. (ii) No reports are available on the 1,3-dipole nature of the *C*-phenylcarbamoyl-*N*-arylhydrazonoyl chlorides **5a**–**d** in the cycloaddition reaction with β-diketones and benzylideneacetone, therefore, we decided to synthesize some derivatives of 3-phenyl carbamyl-pyrazolines and pyrazoles. (iii) To test the effect of different groups on the carbon of the hydrazonoyl chlorides (such as *C*-phenyl-, *C*-ethoxycarbonyl- and *C*-phenyl carbamoyl-) on the regioselectivity of the cycloaddition with benzoylacetone, benzylideneacetone and but-3-en-2-one. The results obtained are used in our re-investigation of the regioselectivity of the 1,3-dipolar cycloaddition of a dipole (**3a**–**d** and **13**) with benzylideneacetone (Scheme 3).

We find that the cycloaddition of hydrazonoyl chloride derivatives of the sodium salts of unsymmetrical β-diketones offers a versatile method for the regioselective synthesis of 2*H*-pyrazoles in a similar fashion to the cycloaddition of nitrilimides with α,β-unsaturated ketones and esters.[4–8]

Fusco[9] has found that the cycloaddition of *C*-ethoxy carbonyl *N*-(*p*-nitrophenyl)hydrazonoyl chloride **3d** with acetylacetone yielded a single pyrazole **4d** and we find a single pyrazole also results from acetylacetone in its reaction with each of several 1,3-dipoles because in this case, only a single enol form reacts (Scheme 1).

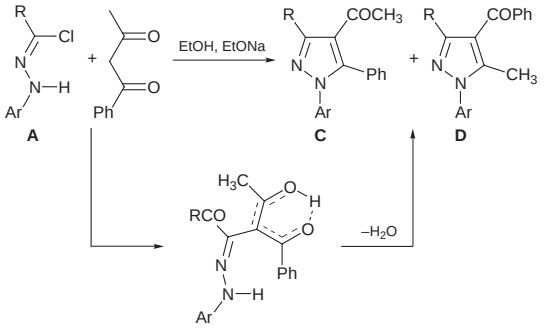


A	B	R	Ar
1a	**2a**	Me	Ph
1b	**2b**	Me	*p*-MeC_6H_4
1c	**2c**	Me	*p*-$NO_2C_6H_4$
3a	**4a**	OEt	Ph
3b	**4b**	OEt	*p*-MeC_6H_4
3c	**4c**	OEt	*p*-BrC_6H_4

A	B	R	Ar
3d	**4d**	OEt	*p*-$NO_2C_6H_4$
5a	**6a**	NHPh	Ph
5b	**6b**	NHPh	*p*-ClC_6H_4
5c	**6c**	NHPh	*p*-BrC_6H_4
5d	**6d**	NHPh	*p*-$NO_2C_6H_4$

Scheme 1

On the other hand, the cycloaddition of the hydrazonoyl chlorides **A** with the sodium salt of benzoylacetone afforded in each case, a mixture of two regioisomeric pyrazoles, *viz*. the 4-acetyl-5-phenyl-3-substituted-1-arylpyrazoles **C** and 4-benzoyl-5-methyl-3-substituted-1-arylpyrazoles **D** in the ratio 9 : 1 to 6 : 4, depending on the nature of the dipolar species used as well as on the reactivity of the two carbonyls in the β-diketone (Scheme 2). The reaction of the 1,3-dipole **1a** with benzoylacetone afforded the regioisomers **7a** and **8a** in ratio 9 : 1.



I, R = CONHPh, Ar = *p*-$NO_2C_6H_4$

A	B	C	R	Ar
1a	**7a**	**8a**	COMe	Ph
1c	**7c**	**8c**	COMe	*p*-$NO_2C_6H_4$
3a	**9a**	**10a**	CO_2Et	Ph
3b	**9b**	**10b**	CO_2Et	*p*-$CH_3C_6H_4$
3c	**9c**	**10c**	CO_2Et	*p*-BrC_6H_4
3d	**9d**	**10d**	CO_2Et	*p*-$NO_2C_6H_4$
5a	**11a**	**12a**	CONHPh	Ph
5b	**11b**	**12b**	CONHPh	*p*-ClC_6H_4
5d	**11d**	**12d**	CONHPh	*p*-$NO_2C_6H_4$
13	**14**	**15**	Ph	Ph

Scheme 2

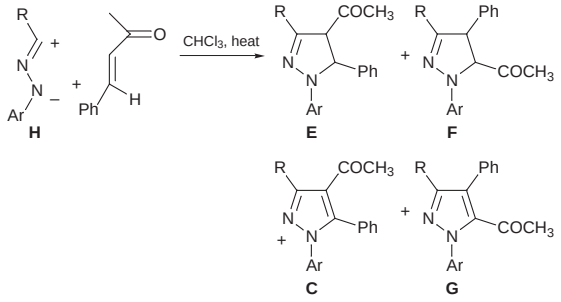
Cycloaddition of *C*-ethoxycarbonyl (**3a**–**c**) and *C*-phenyl carbamoyl *N*-aryl hydrazonoyl chloride derivatives (**5a**,**b**) with benzoylacetone afforded two regioisomeric pyrazoles **9a**–**c**/**10a**–**c** and **11a**,**b**/**12a**,**b** respectively, in the same ratio (7 : 3). The ratio of the regioisomers **9d**/**10d** and **11d**/**12d**, produced from benzoylacetone and the hydrazonoyl chlorides **3d** and **5d**, respectively, was found to be 6 : 4; this difference in ratio may be due to the effect of the nitro group which reduces the nucleophilicity of the nitrogen atom of the hydrazonoyl chloride, thus slowing the attack on both benzoyl and acetyl groups in the intermediates I (Scheme 2).

The chemical shifts of the carbonyl carbon of the acetyl groups in position-4 for 4-acetyl-5-phenyl pyrazole derivatives (**C**) appear in the range at δ (p.p.m.) 196–198, and the methyls of the 4-acetyl groups appear in the ranges at δ 32–31 ppm, but for the 4-benzoyl-5-methyl pyrazole derivatives (**D**) the chemical shifts of the carbonyl carbon of the benzoyl groups and the 5-methyls are found upfield in the range δ 191–193 and 10–13, respectively. These data provide an easy way of distinguishing between the two regioisomeric products, since the chemical shifts in pyrazole

derivatives (**B**), (Scheme 1) are in the range δ 196–198, 32–31 and 11–13, respectively. The assignment of ^{1}H NMR signals for the methyl and the acetyl methyl was confirmed by heteronuclear chemical shift correlation (HETCOR) of the regioisomers **6a** and **7a**.

The cycloaddition of the hydrazonoyl chloride **13** with benzoylacetone afforded two pyrazoles **14** and **15**, isolated by PTLC (Scheme 2). The isolated pyrazole **14** was compared with an authentic sample prepared as in ref. 12.

Cycloaddition of the *C*-ethoxycarbonyl *N*-phenyl hydrazonoyl chloride (**3a**–**c**) (1 eq. mole) with benzylideneacetone (1 eq. mole), in chloroform and triethylamine (1 eq. mole), afforded four products, two pyrazolines (**17a**–**c** and **18a**–**c**), and two pyrazoles (**9a**–**c**, and **19a**–**c**); the ratio of these products, based on ^{1}H NMR analysis, was found to be 2 : 5 : 2 : 1, respectively. The ^{1}H NMR spectra of the crude products showed four singlets at δ 2.34, 2.39, 2.18 and 2.09 for the acetyl groups in compounds **9a**, **17a**, **18a** and **19a**, respectively. The formation of 4-acetyl-5-phenyl- (**9a**–**c**) and 5-acetyl-4-phenylpyrazoles (**19a**–**c**) is due to dehydrogenation taking place during the reaction (Scheme 3). When the crude products were stirred with excess triethylamine in chloroform for two weeks at room temperature, the 5-acetylpyrazoles (**19a**–**c**) and the 4-acetylpyrazoles (**9a**–**c**) were isolated by preparative tlc and compared with authentic samples prepared as in Scheme 2. The reaction of *C*-ethoxycarbonyl *N*-(*p*-nitrophenyl) hydrazonoyl chloride (**3d**) with benzylideneacetone afforded only two products pyrazoline (**18d**) and pyrazole (**9d**) (Scheme 3), in a 1 : 1 ratio, isolated by preparative tlc. The ^{1}H NMR spectrum of the crude products did not show any signals corresponding to the regioisomeric 4-acetyl-3-ethoxycarbonyl-1-(*p*-nitrophenyl)-5-phenyl pyrazoline, as a result of dehydrogenation to pyrazole **9d**.



A	H	E	F	C	G	R	Ar
3a	**16a**	**17a**	**18a**	**9a**	**19a**	EtO_2C	Ph
3b	**16b**	**17b**	**18b**	**9b**	**19b**	EtO_2C	*p*-$CH_3C_6H_4$
3c	**16c**	**17c**	**18c**	**9c**	**19c**	EtO_2C	*p*-BrC_6H_4
3d	**16d**		**18d**	**9d**		EtO_2C	*p*-$NO_2C_6H_4$
5a	**20a**	**21a**	**22a**	**11a**	**23a**	PhNHCO	Ph
5c	**20c**	**21c**	**22c**	**11c**	**23c**	PhNHCO	*p*-BrC_6H_4
13	**24**	**25**	**26**	**14**	**27**	Ph	Ph

Scheme 3

Similar observations were made when the cycloaddition of *C*-phenylcarbamoylnitrile *N*-arylimides (**20a,c**) formed *in situ* from the hydrazonoyl chloride (**5a,c**), respectively, with benzylideneacetone in the presence of triethylamine and chloroform under reflux was studied; four products were obtained, two pyrazolines **21a**,**c** and **22a**,**c** and two pyrazoles **11a**,**c** and **23a**,**c** (Scheme 3) (1 : 5 : 1 3). The formation of 4-acetyl-5-phenyl- (**11a**,**c**) and 5-acetyl-4-phenylpyrazoles (**23a**,**c**) is due to dehydrogenation taking place during the reaction. The reaction mixture was set aside in excess triethylamine and chloroform for seven days at room temperature, and yielded the corresponding pyrazoles **11a**,**c** and **23a**,**c**; the presence of **11a**,**c** in the ^{1}H NMR of the crude material was confirmed by comparison with the ^{1}H NMR spectra of authentic samples prepared as in Scheme 2.

Nuclear Overhauser and exchange spectroscopy (2D) (NOESY) combined with DEPT, HMQC and NMBC prove that the regioisomer **22a** is 5-acetyl-4-phenylpyrazoline. The reaction of BNPI **24** with benzylideneacetone afforded four products, two of which are pyrazolines **25** and **26**; the other two products are the corresponding pyrazoles **14** and **27** (Scheme 3), resulting from dehydrogenation of the pyrazolines **25** and **26** during the reaction and produced in the ratio 14 : 27 : 25 : 24. Gandolfi and Micheli[12] reported that this reaction yielded two pyrazolines **25** and **26** (41 : 59). However, when this reaction mixture was heated under reflux for an extended time, we found that the ratio of the two pyrazolines changed and some pyrazoles, **14** and **27**, were identified by NMR (400 Hz) in the crude material. Dehydrogenation of **25** afforded the corresponding pyrazole **14** which was identical with an authentic sample prepared as shown in Scheme 2.

Finally, we found no effect on the regioselectivity for the formation of 5-acetyl-4-phenyl-3-substituted-pyrazolines when the carbon on the nitrilimides was attached to the phenyl or ethoxycarbonyl or phenylcarbamoyl. This result was also found for the cycloadducts 5-acyl-4-(chiral)alkyl-3-substituted pyrazolines (major product) formed from the cycloaddition reaction of *C*-ethoxycarbonyl *N*-phenyl nitrilimide (**16**) and BNPl (**24**) with 3-alkyl-2-propenoate and 4-alkyl-but-3-en-2-one (α,β-unsaturated enones).[20]

Techniques used: ^{1}H, ^{13}C, DEPT, ^{1}H-^{13}C-COSY, ^{1}H-^{1}H-COLOC and ^{1}H-^{1}H-(2D)-NOESY NMR, IR, mass spectrometry (Ei, FAB and Accurate mass)

References: 24

Tables: 2

Fig. 1: Heteronuclear multiple quantum correlation for pyrazole **22a**

Fig. 2: (*a*) Long range coupling $^2J_{CH}$ and $^3J_{CH}$ in the pyrazole **22a**; (*b*) heteronuclear multiple bond correlation map for **22a**.

Fig. 3: The nuclear Overhauser and exchange spectroscopy (2D) (NOESY) map for pyrazole **22a**.

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