

The Regioselectivity of the 1,3-Dipolar Cycloaddition of α -Carbonylformonitrile *N*-Arylimides to Benzylideneacetone and β -Diketones

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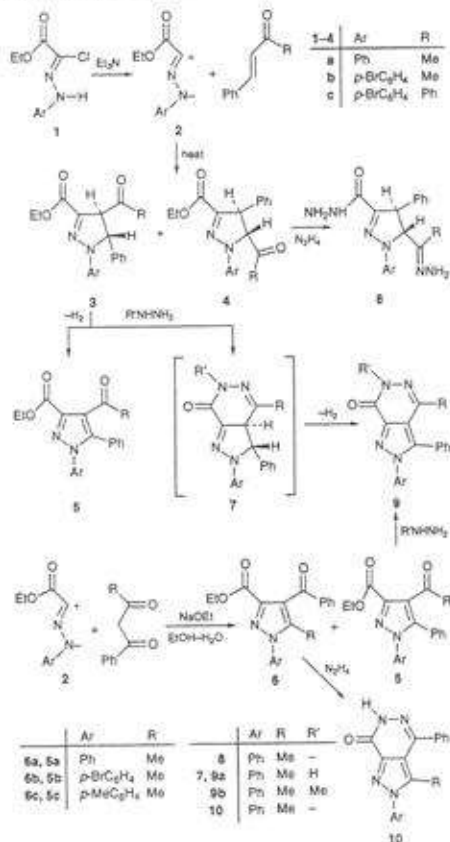
The cycloaddition of the ethoxycarbonylformonitrile *N*-arylimides **2** to benzylideneacetone afforded two regioisomers, 5-acetyl- and 4-acetyl-dihydropyrazoles, but the cycloaddition of **2** to benzoylacetone afforded 4-acetyl- and 4-benzoyl-pyrazole; some pyrazolopyridazin-7-one and pyrazolopyridazine derivatives were also synthesized.

The cycloaddition of the nitrile imide **2** to α,β -unsaturated ketones is regioselective and yields 5-acyl- (or 5-aryloxy) 4-aryl-4,5-dihydro-1*H*-pyrazole derivatives.¹ Tewari and Parihar² have claimed that the cycloaddition of the nitrile imide **2e** to chalcone affords exclusively the corresponding 4-benzoyl-1-(*p*-bromophenyl)-3-ethoxycarbonyl-5-phenyl-4,5-dihydro-1*H*-pyrazole **3c**. Shawali and co-workers³ have found that the above reaction gives a mixture of two regioisomers, viz. **3c** and **4c**. Also, they claimed that the cycloaddition of benzylideneacetone to the nitrile imide **2b**

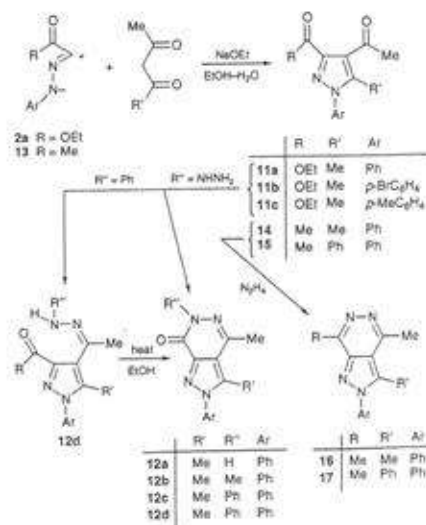
gave one of the two possible regioisomers **4b**. These different results¹⁻³ prompted us to reinvestigate the reactions of the cycloaddition of the nitrile imides **2** with benzylideneacetone and chalcone. Accordingly, we now report the cycloaddition of the nitrile imides **2a-c** and **13** to conjugate bases of active methylene compounds (acetyl- and benzoyl-acetone) as a means of ascertaining the regiostructures of the dihydropyrazoles **3** and **4** and the pyrazoles **5**, **6**, **11**, **14** and **15** through the synthesis of some new derivatives of pyrazolopyridazinones and pyrazolopyridazines.

The cycloaddition of the ethoxycarbonylformonitrile *N*-arylimides **2**, generated *in situ* by treatment of the corresponding *C*-ethoxycarbonyl-*N*-arylimidohydrazoneoyl chloride **1** with triethylamine, with each of chalcone and benzylideneacetone were carried out in refluxing benzene or chloroform. The results show that the reactions studied are regioselective, yielding two possible regioisomers, viz. the 4-benzoyl-5-phenyldihydropyrazole **3c** and its 5-benzoyl-4-phenyl isomer **4c**, and the 1-aryl-4-acetyl-5-phenyldihydropyrazole **3a,b** and its 1-aryl-5-acetyl-4-phenyl isomer **4a,b**, respectively (Scheme 1). In each case, the two cycloadducts were separated by column chromatography.

In contrast, cycloaddition of the nitrile imides **2a-e** with the sodium salt of benzoylacetone afforded in each case a mixture of the two pyrazoles **5a-c** and **6a-c** which were separated by preparative chromatography. The pyrazole **5a**



Scheme 1



Scheme 2

was also obtained from the dihydrogenation of **3a** by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as dehydrogenation agent. The structure of the cycloadduct **3** was substantiated further by the fact that treatment of **3a** with hydrazine hydrate in refluxing ethanol afforded the pyrazolo[3,4-*d*]pyridazin-7-one derivative **7**. However, similar treatment of **4a** gave the hydrazide **8**. Oxidation of **7** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded the pyrazolo[3,4-*d*]pyridazin-7-one derivative **9a**, which was also obtained from the reaction of the pyrazole **5a** with hydrazine hydrate. Similarly, reaction of the pyrazole **6** with hydrazine hydrate afforded the pyrazolo[3,4-*d*]pyridazin-7-one derivative **10** (Scheme 1). It is known⁸ that the cycloaddition of 1,3-dipolar nitrile imides to the enol form leads to regioselective 4-aryl- (or 4-acetyl-) pyrazoles. However, in our case the formation of the two regioisomers **5** and **6** formed from the reaction of **2** with benzoylacetone can be explained on the basis that two different enols are formed during the reaction. These results support the possible mechanism reported in the literature.⁷ Both of the regioisomers **5** and **6** obtained above suggest that the carbanion, acting as a base, reacts with **1** to form a nitrile imide dipole **2**. The latter then adds to the two possible enols of the benzoylacetone to give the two regioisomers **5** and **6** after subsequent loss of water.

Nevertheless, the cycloaddition of the nitrile imides **2a-e** to the sodium salt of acetylacetone produced in each case only one isomer, a 4-acetyl-3-ethoxycarbonyl-5-methyl-1-arylpyrazole **11a-c**, because in this case, there is no possible formation of different enols. Further evidence for the structure of the regioisomer **11a** was obtained by its reaction with hydrazine derivatives which led to the pyrazolo-pyridazin-7-one derivatives **12a-e** (Scheme 2).

The above method was used to synthesize some new pyrazolopyridazine derivatives **16** and **17**, as follows. The

cycloaddition of the C-acetyl-N-phenyl nitrile imide **13** to the sodium salts of acetylacetone and benzoylacetone yielded, in each case, one regioisomer, viz. the 4-acetyl-5-methyl-**14** and 4-acetyl-5-phenyl-pyrazole **15**, respectively. Treatment of the pyrazoles **14** and **15** with hydrazine hydrate in refluxing ethanol yielded the pyrazolopyridazines **16** and **17**, respectively (Scheme 2).

Techniques used: NMR (¹H and ¹³C), IR, mass spectrometry

References: 11

Table 1: IR and ¹H/¹³C NMR data for 4,5-dihydro-1H-pyrazole¹⁰

Table 2: Physical properties and elemental analyses for dihydropyrazoles

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