Synthesis of Novel Spiro and Fused Cyclopenta[*c*]-pyrazole and -pyrimidine Derivatives

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Condensation of diarylmethylidenecyclopentanes with hydrazine, hydroxylamine and thiourea derivatives afford the corresponding fused pyrazoles, oxazoles and pyrimidines.

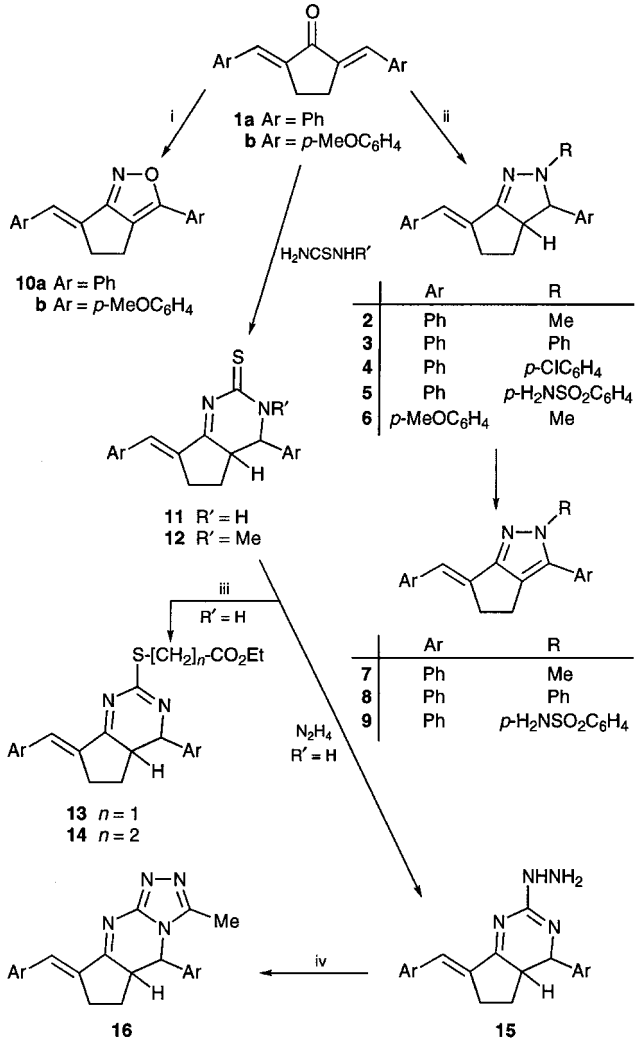
Nitrile imides are well known 1,3-dipoles and their reactions with α,β-unsaturated carbonyl compounds,[1–4] 4-arylmethylideneoxazolones[5,6] and 3-arylmethylidene lactones[7] have been extensively investigated. On the other hand, it has been reported that 2-substituted 5-methylidenecyclopentan-2-ones are useful as intermediates for the synthesis of cyclopentenoid antibiotics and anticancer agents.[8]

For these reasons some new fused cyclopentapyrazole, cyclopentapyrimidine and spiropyrazoline derivatives have been synthesized either by the 1,3-dipolar addition of nitrile imides to arylmethylidenecyclopenta[*c*]pyrazole derivatives **2–6** or by other methods, with the two-fold objective of preparing compounds of biological importance and studying the regiochemistry of the cycloaddition process.

The condensation of substituted hydrazines with the diarylmethylidenecyclopentanones **1a**,**b** afforded 2,3-disubstituted 6-arylmethylidenecyclopenta[1,2-*c*]pyrazoles **2–6**. Mild oxidation of **2**, **3** and **5** with bromine water gave the corresponding pyrazoles **7**, **8** and **9** respectively. Condensations of hydroxylamine with α,β-unsaturated ketones usually yield the corresponding isoxazolines, but in some cases the product was found to be the isoxazole derivative.[9] However, in our case the reactions of **1a**,**b** with hydroxylamine yielded the corresponding isoxazole derivatives **10a**,**b** (Scheme 1).

In view of the usefulness of 2-sulfanyl-1,4-dihydropyrimidines as vulcanizing accelerator agents and photographic stabilizers,[10] we prepared some new pyrimidine derivatives **11** and **12** from the condensation of **1a** with thiourea and methylthiourea. The reaction of **11** with bromoesters afforded the thioesters **13** and **14**, while reaction with hydrazine hydrate afforded the 2-hydrazino derivative **15** which on condensation with acetylacetone in refluxing ethanol gave the triazolo derivative **16** (Scheme 1).

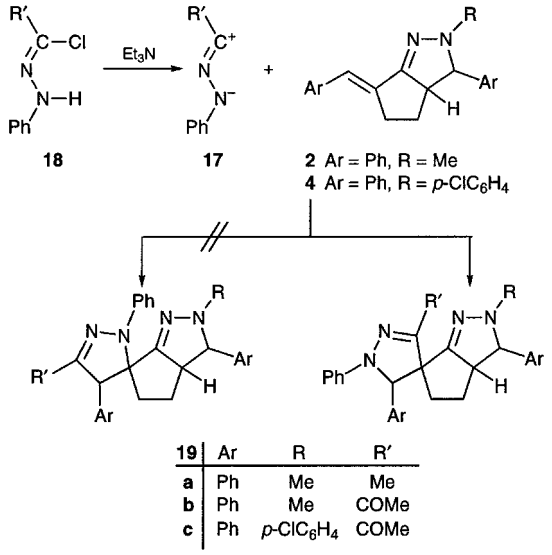
The reactions of the nitrile imides **17**, generated *in situ* by treatment of the corresponding hydrazonoyl chlorides **18** with triethylamine, with arylmethylidenecyclopentanes **2** and **4c** were carried out in refluxing toluene. TLC analysis of the reaction mixture on silica gel with a mixture of light petroleum and ethyl acetate (5:1 v/v) as eluent showed the formation of only one product. This was confirmed by ^{1}H NMR analysis of the crude reaction product, in which only one methine singlet signal was observed. These findings indicate that the reactions studied are regiospecific, yielding one of the two possible regioisomers **19** and **19′**.



	Ar	R
2	Ph	Me
3	Ph	Ph
4	Ph	*p*-ClC$_6$H$_4$
5	Ph	*p*-H$_2$NSO$_2$C$_6$H$_4$
6	*p*-MeOC$_6$H$_4$	Me

	Ar	R
7	Ph	Me
8	Ph	Ph
9	Ph	*p*-H$_2$NSO$_2$C$_6$H$_4$

Scheme 1 *Reagents:* i, NH_2OH; ii, $RNHNH_2$; iii, $Br[CH_2]_nCO_2Et$; iv, $(CH_3CO)_2CH_2$



19	Ar	R	R′
a	Ph	Me	Me
b	Ph	Me	COMe
c	Ph	*p*-ClC$_6$H$_4$	COMe

Scheme 2

Techniques used: ^{1}H NMR, MS, IR, elemental analysis

References: 12

Table 1: Physical and elemental analytical data for pyrazoline and pyrazole derivatives

Table 2: ^{1}H NMR spectral data for the prepared compounds

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