Difunctional Heterocycles: a Convenient Synthesis of Bis(4,5-dihydropyrazolyl) Ethers from their Precursor Bis(chalcones)

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Bis(4,5-dihydropyrazolyl) ethers **18–22**, **26**, **27** and **40–44** are obtained in 35–80% yield by heating the corresponding bis(chalcones) **13–17** and **34–37** with each of hydrazine hydrate and phenylhydrazine in refluxing acetic acid.

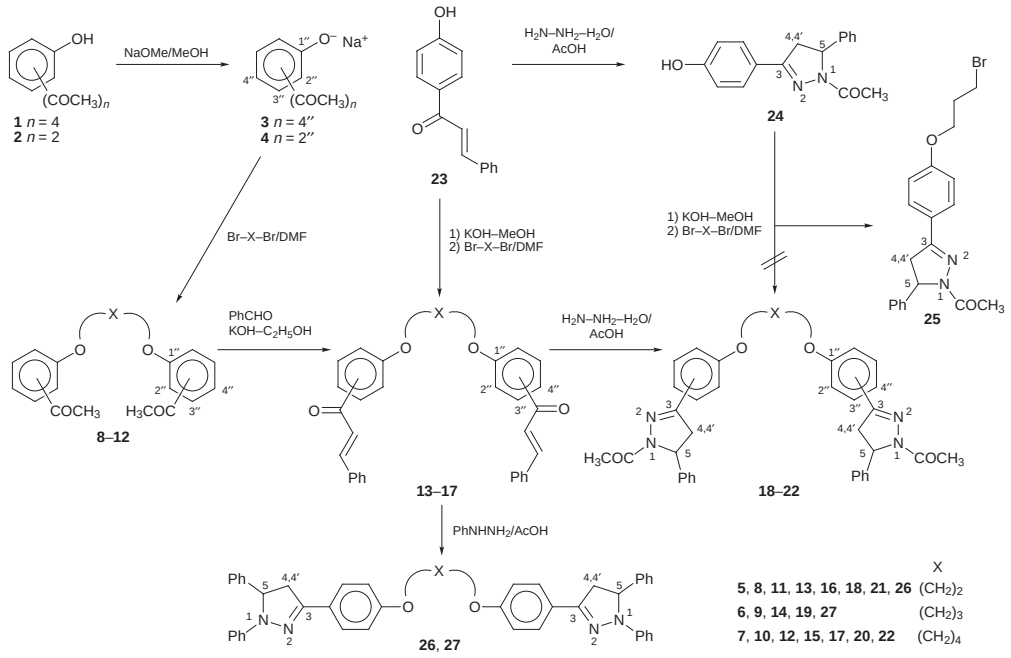
The synthesis of 2-pyrazolines has received considerable attention because of their wide range of applications. Thus substituted 2-pyrazolines have found applications as activators for polymerization,[1] dyes for wool, nylon,[2] as electrophotographic photoconductors,[12] and as wavelength shifters in liquid and polymer scintillation.[13] There is also continuous interest in the chemistry of pyrazoles on account of their associated important biological properties. For example studies have revealed that substituted pyrazole derivatives exhibit (analgesic, antipyretic, hyperglycenic),[18] antiinflammatory,[19] and antidepressant activity.[23]

In connection with these findings and the report that many biologically active natural and synthetic products have molecular symmetry,[28] this project is directed towards the synthesis of some new isomeric bis(4,5-dihydropyrazol) derivatives of expected potential applications. We have also studied the effect of the generated asymmetric centre in the pyrazole moiety of the new isomeric derivatives on their ^{1}H NMR and ^{13}C NMR spectra.

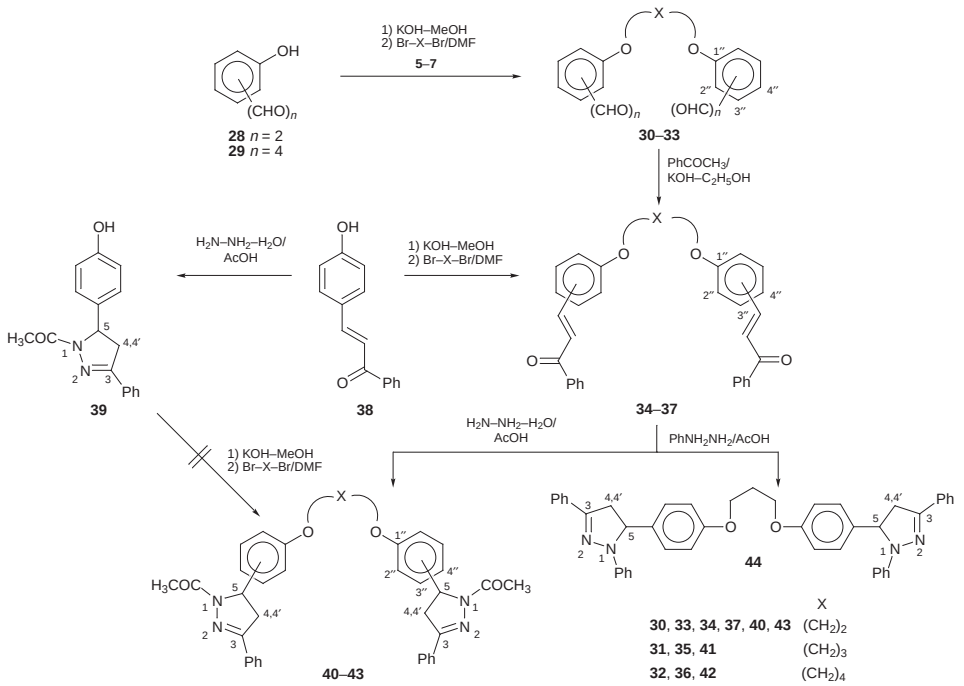
Our strategy to synthesize the new bis(4,5-dihydropyrazol) derivatives **18–22**, **26** and **27** is outlined in Scheme 1. Thus reaction of each of the sodium salts **3** and **4** (obtained upon treatment of each of 4-hydroxyacetophenone **1** and 2-hydroxyacetophenone **2** respectively with sodium ethoxide in ethanol) with the appropriate dibromoalkane **5–7** in boiling DMF afforded the corresponding bis(acetyl) ethers **9–12** respectively. The latter underwent basic condensation with benzaldehyde to give the corresponding bis(cinnamoyl) ethers **13–17** in 65–80% yield. Condensation of compounds **13–17** with each of hydrazine hydrate and phenylhydrazine in refluxing acetic acid afforded the corresponding bis(4,5-dihydropyrazolyl) ethers **18–22** in 60–80% yield and **26**, **27** in 35–45% yield respectively. The bis(cinnamoyl) ethers **14** and **15** were alternatively obtained in 32 and 40% yield respectively by reacting the potassium salt of 4-cinnamoylphenol **23** with each of 1,3-dibromopropane **6** and 1,4-dibromobutane **7** respectively. Condensation of **23** with hydrazine hydrate in acetic acid afforded the corresponding 4,5-dihydropyrazole **24** in 63% yield. Attempts to react **24** with 1,4-dibromobutane in order to obtain the corresponding bis(pyrazolyl) ether **20** were unsuccessful and the reaction gave instead the corresponding monoalkylated product 4,5-dihydro-1H-3-(4-bromobutyloxyphenyl)pyrazole **25** in 45% yield.

Our study was extended to include the synthesis of the new bis(4,5-dihydropyrazolyl) ethers **40–44** (Scheme 2).

Thus the reaction of the potassium salt of **28** and **29** (obtained upon treatment of 4-hydroxybenzaldehyde and salicylaldehyde respectively with methanolic KOH) with the appropriate dibromoalkane in DMF afforded the corresponding bis(2-carbonyl) ethers **30–33**.[31,32] The latter underwent base catalyzed condensation with acetophenone to give the corresponding bis(benzoylvinyl) ethers **34–37**



Scheme 1 Position of acetyl, cinnamoyl and pyrazolyl substituents: 4″ in **8–10**, **13–15** and **18–20**; 2″ in **11**, **12**, **16**, **17**, **21** and **22**



Scheme 2 Position of acetyl, cinnamoyl and pyrazolyl substituents: 4″ in **30**–**32**, **34**–**36** and **40**–**42**; 2″ in **33**, **37** and **43**

in 65–80% yield. Compounds **35** and **36** were alternatively obtained in 35 and 44% yield respectively by reacting the potassium salt of 4-benzoylvinylphenol **38** (obtained upon treatment of **38** with methanolic KOH) with each of 1,3-dibromopropane **6** and 1,4-dibromobutane **7** respectively in boiling DMF. Condensation of compounds **34**–**37** with hydrazine hydrate in acetic acid afforded the corresponding bis(1-acetyl-4,5-dihydro-3-phenyl-1H-pyrazol-5-yl)ethers **40**–**43** in 55–70% yield. Attempts to obtain compounds **40**–**42** by alkylation of compound **39** with the appropriate dibromoalkane were unsuccessful. Compound **39** was obtained in 65% yield by reacting **38** with hydrazine hydrate in acetic acid. Similarly, condensation of compound **35** with phenylhydrazine in acetic acid led to the formation of the corresponding 1,3-bis[4-(1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)phenoxy]propane **44** in 30% yield.

Numerous studies have been undertaken to establish the mode of addition of hydrazine derivatives to chalcones.[35,38] The structure of all compounds was confirmed by ^{1}H NMR, ^{13}CNMR and mass spectra.

From the ^{1}H NMR and the ^{13}C NMR spectra of the bis(chalcones) **11**–**15**, **34**–**37** and the bis(pyrazolyl) ethers **18**–**22**, **26**, **27**, **40**–**44** the following conclusions were made: (1) The *E*-configurations were assigned to the olefinic protons of the cinnamoyl moiety in the bis(chalcones) **13**–**15** and **34**–**36**. (2) The magnetically non-equivalent protons in the pyrazole ring of compounds **18**–**22**, **26**, **27** and **40**–**44** suggest the generation of an asymmetric centre in these molecules. (3) The appearance of the OCH_2 resonance as a multiplet in compound **43** together with the fact that its precursor **37** exhibits a singlet for these protons suggests that the generated asymmetric centre (in the pyrazole ring) is close enough to this CH_2 group. On the other hand, the asymmetric centre generated in **18**–**22**, **40**–**42** and **44** is not close enough to the OCH_2 to effect such splitting. (4) Evidence from the ^{13}C NMR data for compound **43** indicate that it exists entirely as one stable conformer. Similar results have been reported by us for some bis(dihydro-oxadiazolyl) ether derivatives.[42]

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Techniques used: ^{1}H NMR, ^{13}C NMR, MS

References: 44

Schemes: 2

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