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Efficient syntheses of 2-(2,6-dichloro-4-trifluoromethyl-phenyl)tetrahydrocyclopenta, tetrahydrothiopyrano, hexahydrocycloheptapyrazoles and tetrahydroindazoles

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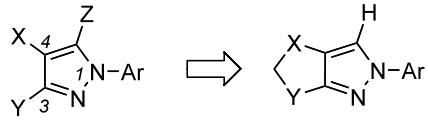
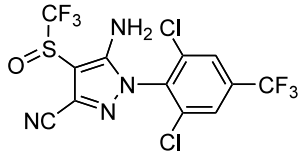
Abstract—Two methods are described for the regiospecific synthesis of 3,4-fused-cycloalkyl-1-arylpyrazoles; the key step is the reaction between aryl hydrazines and cyclic α-(dimethoxymethyl)ketones. The latter are obtained by BF_3-promoted alkylation of ketones with trimethylorthoformate.

The pyrazole ring system represents an important template that has attracted considerable interest in the search for novel pharmaceuticals and agrochemicals.[1] 1-Phenyl pyrazoles have recently appeared in several drug candidates for treating various diseases e.g. Cox-2 inhibitors (Searle Co), IL-1 synthesis inhibitors (Smith Kline Beecham Co.) and protein kinase inhibitors (Hoffmann LaRoche Co.) etc. Pyrazoles bearing carbonyl or nitrile functionalities at the *4* position exhibit a range of interesting biological activities. In particular, 1-arylpyrazoles (generic structure **1**) are potent and selective γ-aminobutyric acid (GABA)-gated chloride channel antagonists, and have recently emerged as a class of agrochemicals of economic importance.[2] Fipronil (**3**), the active ingredient of the antiflea agent Frontline®, is an excellent example of a phenyl pyrazole with insect GABA gated chloride channel antagonistic properties.

In connection with our research program on antagonists of the GABA channel we were interested in synthesizing 2-(2,6-dichloro-4-trifluoromethyl-phenyl)tetrahydrocyclopenta, tetrahydrothiopyrano, hexahydrocycloheptano pyrazoles and tetrahydroindazoles which represent in part rotationally constrained analogs of anti-flea agent fipronil. Other ring related fused pyrazoles have been reported. For example, 2-aryl-4,5,6,7-tetrahydroindazoles which are cyclohexanefused phenylpyrazoles have been reported to inhibit protoporphyrinogen oxidase (PPO), an enzyme which catalyzes the oxidation of protoporphrinogen to protoporphyrin and is the site of action of membrane disrupting herbicides.[3,4]



1 **2**



3

Several syntheses of isomeric 4,5-fused bicyclic pyrazoles have been reported.[5] However, the development of regioselective methods leading to 3,4-fused cycloalkylpyrazoles has received less attention, especially when targeting 5-unsubstituted pyrazoles. We report an efficient, versatile and convenient synthetic

Keywords: arylpyrazoles; synthesis; alkylation; boron trifluoride; trimethylorthoformate.

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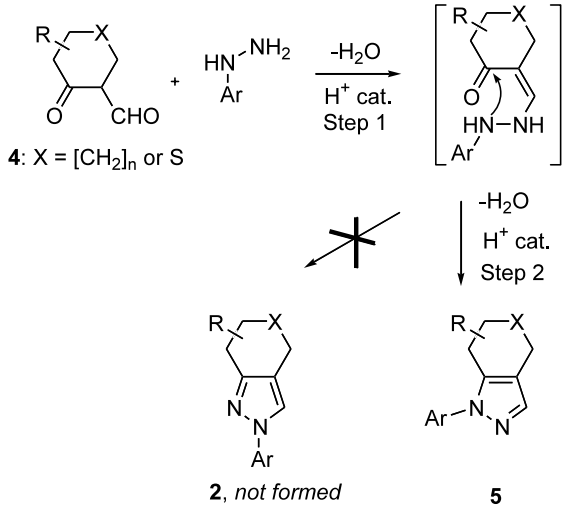
routes, which provide rapid access to 2-(2,6-dichloro-4-trifluoromethyl-phenyl)tetrahydrocyclopenta, tetrahydrothiopyrano, hexahydrocycloheptano pyrazoles and tetrahydroindazoles.

Synthetic entries into the desired 3,4-bicyclic system are typically multi-step sequences based on the condensation of an arylhydrazine and cyclic β-cyanoketones or β-ketoesters.[6] The 5-amino- or 5-hydroxypyrazoles obtained, respectively, requires an additional deamination or deoxygenation step to provide the 5-unsubstituted 3,4-cycloalkylpyrazoles. Although a one-pot synthesis of 2-substituted 2,4,5,6-tetrahydrocyclopentapyrazoles has been reported recently, the required (triphenylphosphenyl- ideneaniline and 2-azido-1-cyclopentene-carboxaldehyde) starting materials are not easily accessible.[7]

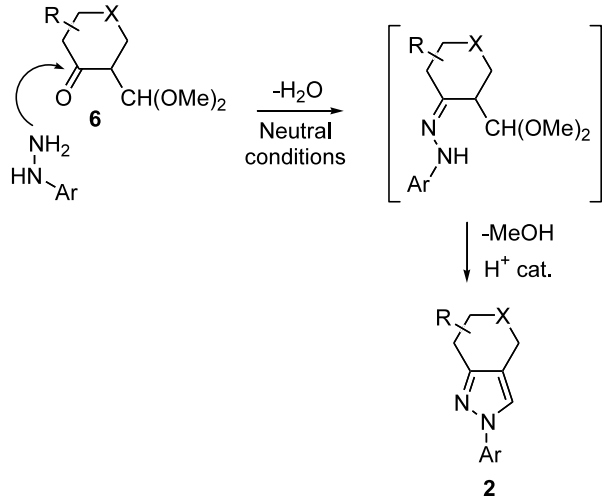
The cyclocondensation of hydrazines with ketoaldehydes under acidic conditions generally leads to 4,5-cycloalkyl pyrazoles (**5**). The regioselectivity of these reactions is determined by the first condensation step, where under acid catalysis the more-reactive aldehyde and the terminal NH_2 group of the arylhydrazine react first leading to formation of product (**5**) (Scheme 1).

In order to revert the regiochemistry of the condensation reaction we explored a strategy by which the more-reactive aldehyde in the starting β-formylcycloalkanone was masked as a dimethylketal (**6**), and the first step in the condensation was carried out under neutral conditions to avoid in situ cleavage of the acetal group to the aldehyde (Scheme 2).

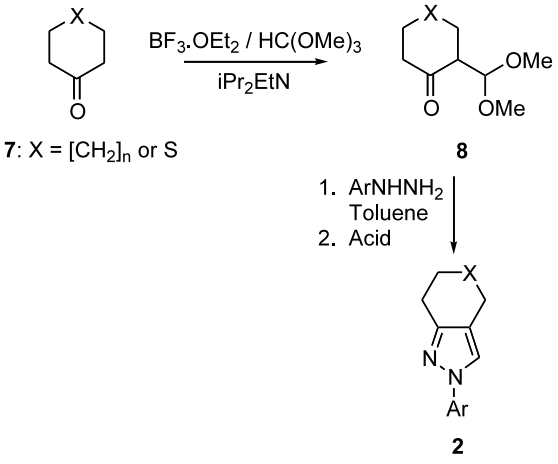
The required α-(dimethoxymethyl)cycloalkanones (**6**) were obtained by two different methods from the appropriate cycloalkanones. In method A, a *symmetric* cycloalkanone (**7**) was reacted with trimethylorthoformate in the presence of $BF_3{\cdot}OEt_2$ to obtain an α-(dimethoxymethyl)ketone intermediate (**8**), which was directly used in the subsequent condensation reaction[8] (Scheme 3).



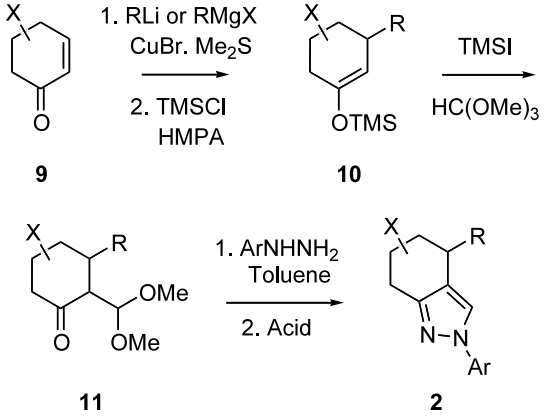
Scheme 1. Reaction pathway for the formation of 4,5-cycloalkylpyrazoles.



Scheme 2. Reaction pathway for the formation of 3,4-cycloalkylpyrazoles.



Scheme 3. Synthetic route used with symmetric cycloalkanones for the formation of 3,4-cycloalkylpyrazoles.



Scheme 4. Synthetic route used with asymmetric cycloalkanones for the formation of 3,4-cycloalkylpyrazoles.

For the preparation of pyrazoles derived from *nonsymmetrically* substituted cycloalkanones method B was developed. In this case, the kinetic enolates were regiospecifically generated by reacting α,β-unsaturated

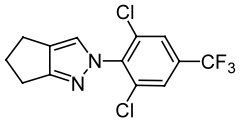
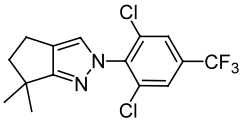
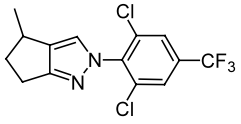
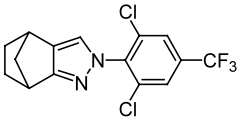
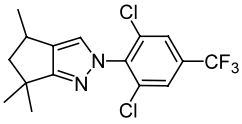
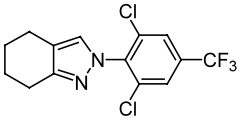
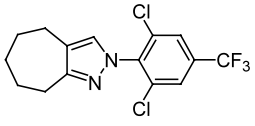
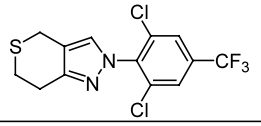
cycloalkanones (**9**) with either organolithium or Grignard reagents in the presence of $CuBr{\cdot}Me_2S$, followed by trapping the resulting enolate with chlorotrimethylsilane as silyl enol–ethers (**10**). The crude enol–ethers were then reacted with trimethylorthoformate in the presence of catalytic amounts of iodotrimethylsilane at −78°C to obtain α-(dimethoxymethyl)cycloalkanone intermediates (**11**) regiospecifically (Scheme 4).[9]

The crude α-(dimethoxymethyl)cycloalkanone (**8**) or (**11**) was reacted with hydrazine in benzene at reflux temperature for 2 h with azeotropic removal of water to obtain the corresponding ketimine, which was then cyclized under acid catalysis to furnish the desired 1-phenylpyrazole **2** in good overall yields (Table 1).

Conclusions

We have combined two regiospecific processes, namely the α-(dimethoxy)methylation of ketones with trimethyl-orthoformate promoted by $BF_3{\cdot}OEt_2$ followed by a condensation–deprotection–condensation sequence, to provide rapid access to a number of 3,4-fused-cycloalkyl-1-arylpyrazoles. This methodology has been extended to thiocycloalkanones, furnishing a facile entry into novel 3,4-fused-cycloheteroalkylpyrazoles and related compounds of potential biological and medicinal interest. The overall sequence yields are moderate to good, and amenable to multi-gram scale preparations. In addition this methodology provides specific regiochemical control in the cyclocondensation step with specific substitutions on cycloalkyl ring system from readily available staring materials.

Table 1. 3,4-Fused-cycloalkyl-1-arylpyrazoles prepared by methods A or B via Scheme 1

Entry	Product	Method	Yield %
1		A	54
2		A	64
3		B	64
4		A	52
5		A	50
6		A	57
7		A	48
8		A	53

[a] For experimental conditions see General Procedures. Yields are for isolated products from the corresponding starting ketone after chromatography on Silica. All reaction products characterized by MS and ^1H NMR spectroscopy and are >95% pure by NMR and TLC.

General procedures

Method A. A solution of $BF_3{\cdot}OEt_2$ (7.5 mL, 0.06 mol) in CH_2Cl_2 (20 mL) was added dropwise with stirring to 5.5 mL (0.05 mol) of trimethylorthoformate at −30°C under N_2 over a period of 10 min. The reaction mixture was then allowed to warm to 0°C. After 15 min at this temperature the reaction mixture was cooled back to −78°C. A solution of the corresponding ketone (0.025 mol) in CH_2Cl_2 (10 mL) was then added, followed by diisopropylethyl amine (0.075 mol) over 30 min. The resulting mixture was stirred at −78°C for 1 h and poured into cold $NaHCO_3$ (saturated solution, 500 mL) and CH_2Cl_2 (200 mL) with vigorous stirring. The organic phase was separated, washed with water (3×100 mL), dried and concentrated to obtain the β-dimethoxymethylketone that was used directly for the condensation step.

Method B. To a solution of $CuBr{\cdot}Me_2S$ in THF (10 mL) at −30°C was added the Grignard or organolithium reagent (2 mmol). The resulting solution was stirred at −30°C for 1 h and cooled back to −78°C. HMPA (0.17 mL, 2 mmol) was added dropwise, followed by a mixture of α,β-unsaturated cycloalkanone (1 mmol) and TMSCl (0.24 mL, 2.4 mmol). The resulting mixture was stirred for 30 min at −78°C. and warmed to −40°C for 30 min. The reaction was quenched by addition of triethylamine (0.69 mL, 5 mmol), followed by a mixture of ether–hexane (1:1, 10 mL) and water (1 mL). The resulting mixture was allowed to warm to room temperature and passed through Celite, eluting with ether (3×5 mL). The organic fractions were combined, dried and concentrated in vacuo to obtain the corresponding silyl enol–ether, which was used directly in the next step. TMSI (0.01 mL, 0.1 mmol) was added to a solution of silyl enol–ether (1.2 mmol) and trimethylorthoformate (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL) at −78°C under a N_2 atmosphere. The resulting mixture was stirred at −78°C for 1 h and poured into ice cold saturated $NaHCO_3$ (10 mL). The organic layer was separated, dried and concentrated to obtain the corresponding α-(dimethoxymethyl)ketone.

Condensation of α-(dimethoxymethyl)ketones with arylhydrazine for the synthesis of fused 1-arylpyrazoles. β-(Dimethoxymethyl)ketones (1 mmol) and arylhydrazine (1 mmol) in benzene (10 mL) was heated at reflux with azeotropical removal of water. After the starting mate-

rials were consumed the reaction mixture was allowed to cool to room temperature and concentrated to obtain a thick oil which was dried under high vacuum for 1 h. The resulting residue was redissolved in EtOH and few drops of conc. HCl were added and heated at 80°C for 20 min. The reaction mixture was allowed to cool to room temperature and poured in to ice cold satd $NaHCO_3$. The product was then extracted in to CH_2Cl_2 and purified by column chromatography.

Acknowledgements

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References

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9. Analytical data for representative new compounds in Table 1:
   Entry 1: NMR ($CDCl_3$) δ 7.73 (s, 2H), 7.15 (s, 1H), 2.86 (t, $J=7.2$ Hz, 2H), 2.78 (t, $J=7.2$ Hz, 2H), 2.51 (m, 2H)); MS (M^++1) 322.4
   Entry 4: NMR ($CDCl_3$) δ 7.75 (s, 2H), 7.08 (s, 1H), 3.48 (d, $J=7.4$ Hz, 2H), 2.1 (d, $J=7.0$ Hz, 1H), 1.97 (d, $J=7.0$ Hz, 1H), 1.86 (d, $J=7.0$ Hz, 1H), 1.30 (m, 3H) MS: (M^++1) 348.3
   Entry 8: NMR ($CDCl_3$) δ 7.68 (s, 2H), 7.18 (s, 1H), 2.89 (t, $J=7.2$ Hz, 2H), 2.84 (s, 2H), 2.67 (t, $J=7.2$ Hz, 2H); MS (M^++1) 354.3.