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Montmorillonite KSF clay-promoted synthesis of enantiomerically pure 5-substituted pyrazoles from 2,3-dihydro-4*H*-pyran-4-ones

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Abstract—2,3-Dihydro-4*H*-pyran-4-ones derived from D-glucal undergo rapid condensation with aryl hydrazines in the presence of montmorillonite KSF clay under mild conditions to afford a novel class of chiral 5-substituted pyrazoles in good yields with high selectivity. The stereochemical assignments of the products were achieved by NMR studies.

The pyrazole moiety is a core structure in a number of biologically active compounds.[1] Many pyrazole derivatives are known to exhibit a wide range of biological properties such as anti-hyperglycemic, analgesic, anti-inflammatory, anti-pyretic, anti-bacterial, hypoglycemic and sedative-hypnotic activity.[2] In particular, arylpyrazoles are important in medicinal and pesticide chemistry.[3] Recently, some arylpyrazole derivatives were reported to have non-nucleoside HIV-1 reverse transcriptase inhibitory activity.[4] Extensive studies have been devoted to arylpyrazole derivatives such as celecoxib, the well-known cyclooxygenase-2 inhibitor.[5] Thus continuous efforts have been made towards the development of more general and versatile synthetic methods for the synthesis of pyrazoles.[2] However, there are no reports on the synthesis of pyrazoles from chiral pyranones derived from D-glucal. Recently, the use of solid acids such as clays, zeolites, and ion-exchange resins has achieved importance in organic chemistry.[6] Generally heterogeneous solid acids are advantageous over conventional homogeneous acid catalysts as they can be easily recovered from the reaction mixture by filtration and can be reused after activation or without activation making the process economically viable.[7] In many cases, heterogeneous catalysts can be recovered with only minor changes in activity and selectivity so that they can be used in continuous flow reactions. Among heterogeneous catalysts, clays are attractive because of their low cost, reusability, flexibility in their acid strength, ease of handling, environmental compatibility, nontoxicity and experimental simplicity.[8]

In continuation of our research programme on the use of clays for organic transformations,[9] we report herein a novel method for the synthesis of enantiomerically pure 5-substituted pyrazoles from 2,3-dihydro-4*H*-pyran-4-ones and aryl hydrazines using the inexpensive montmorillonite KSF clay as a reusable solid acid catalyst. Thus treatment of 2,3-dihydro-4*H*-pyran-4-one **1** with phenyl hydrazine **2b** in the presence of montmorillonite KSF clay afforded the optically active 1,3-di(benzyloxy)-1-(1-phenyl-1*H*-5-pyrazolyl)-(1*S*,2*R*)-propan-2-ol **3b** in 80% yield (Scheme 1).

Similarly various phenyl hydrazines such as 2,5-dichloro-, 2-ethyl-, 4-chloro-, 3-chloro- and 4-methyl analogues reacted smoothly with 2,3-dihydro-4*H*-pyran-4-one to give the corresponding 5-substituted pyrazole derivatives in good yields (Table 1, entries **c**–**g**). In all cases, the reactions were carried out using ethanol as the solvent. The reactions proceeded efficiently under refluxing conditions. Analogous to phenyl hydrazine, hydrazine hydrate also afforded the respective pyrazole in good yield (Table 1, entry **a**).

The presence of a hydroxyl group in the product **3** (R = 2,5-dichlorophenyl) was confirmed by conversion to the acetate derivative **4** (R = 2,5-dichlorophenyl), (Scheme 2).

Keywords: Glycals; Dihydropyranones; Hydrazines; Pyrazoles.
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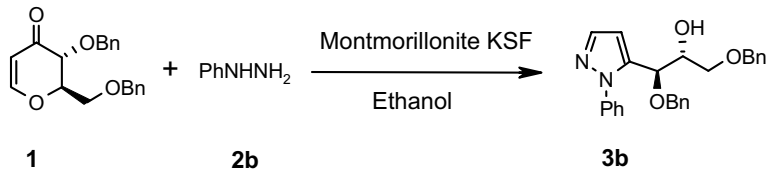
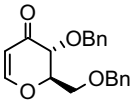
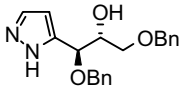
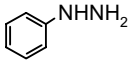
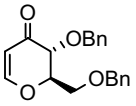
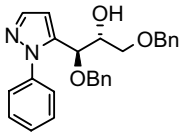
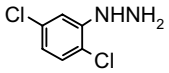
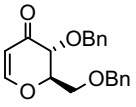
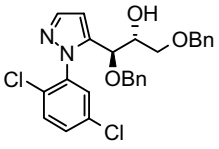
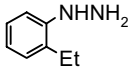
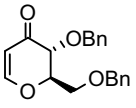
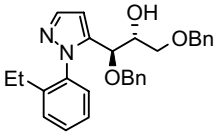
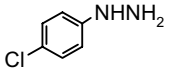
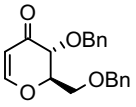
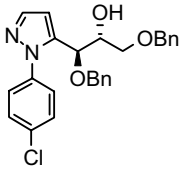
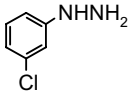
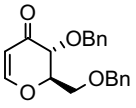
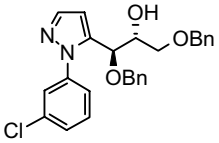
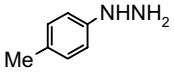
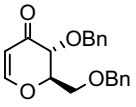
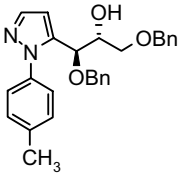
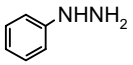
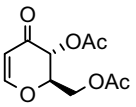
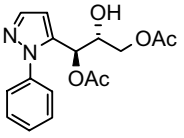
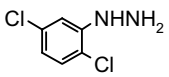
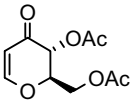
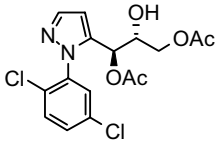


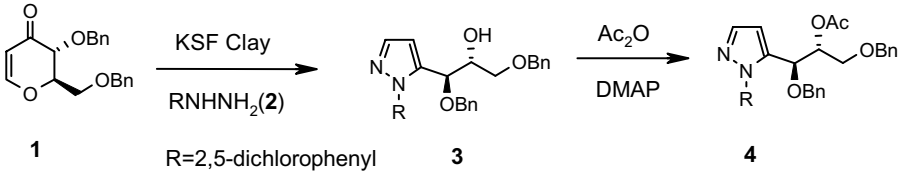
1 2b 3b

Scheme 1.

Table 1. Synthesis of pyrazoles from aryl hydrazines and dihydropyranones

Entry	Aryl hydrazine	Dihydropyranone	Product[a]	Reaction time (h)	Yield (%)[b]
a	$NH_2NH_2{\cdot}H_2O$			5.5	78
b				6.0	80
c				4.5	85
d				5.5	82
e				4.5	86
f				6.0	81
g				5.5	79
h				6.5	60
i				7.5	57

[a] Products were characterized by ^1H NMR, ^{13}C NMR, IR and spectroscopy.
[b] Yield refers to pure products after chromatography.



Scheme 2.

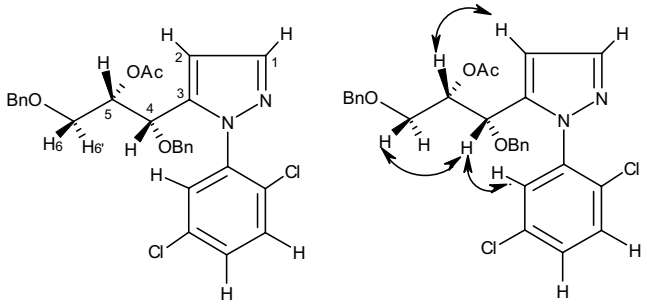


Figure 1. Chemical structure and characteristic NOE's of product **4**.

The assignment of the structure of the product **4** was achieved by incisive NMR studies such as NOESY and HSQC experiments. The HSQC and ^{13}C spectra clearly showed the presence of 28 carbons with 1-methyl, 3-methylenes, 17-methines and 7-quaternary carbons for product **4**. The NOE cross peaks between H6 and H4, H4 and Ha, and H5 and H2 confirmed the structure as **4** (Fig. 1).

The reaction probably proceeds via the formation of an *N*-glycoside followed by intramolecular pyran ring opening and subsequent cyclization of the –NH with the keto group to result in the formation of the 5-substituted pyrazole (Scheme 3).

In the absence of the clay, no reaction was observed between the pyranones and aryl hydrazines. Among various acid catalysts such as $Sc(OTf)_3$, $Yb(OTf)_3$, $Ce(OTf)_3$, $In(OTf)_3$ and $InCl_3$, montmorillonite KSF was found to be superior in terms of conversion and reaction times. However, similar results were obtained using 10 mol% of *p*-toluenesulfonic acid as catalyst. As solvent, ethanol gave the best results. Although, this reaction proceeds smoothly in commercial grade ethanol (containing about 0.2% of water), the reaction in water alone was unsuccessful. The scope and generality of this process was illustrated with respect to various aryl hydrazines and pyranones and the results are presented in Table 1.[10] The catalyst was recovered by simple filtration and reused three times without any significant decrease in activity after being washed with methanol and activated at 120 °C. Thus, the use of this reusable solid acid makes this method quite simple, convenient and economically viable.

In conclusion, we have described a novel and efficient protocol for the synthesis of enantiomerically pure pyrazoles from 2,3-dihydro-4*H*-pyran-4-ones and phenyl hydrazines using the inexpensive and readily available solid acid, montmorillonite KSF clay. The simple experimental and product isolation procedures combined with ease of recovery and recyclability of the clay is expected to contribute to the development of green strategies for the synthesis of highly functionalized pyrazole derivatives.

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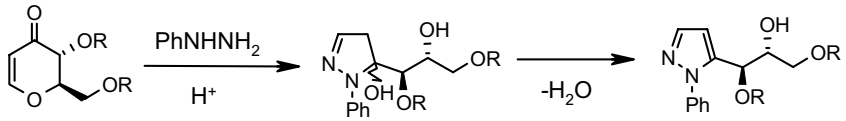

Scheme 3.

9. (a) Yadav, J. S.; Reddy, B. V. S.; Sadashiv, K.; Reddy, P. S. R. *Tetrahedron Lett.* **2002**, *43*, 3853; (b) Yadav, J. S.; Reddy, B. V. S.; Balanarsaiah, E.; Raghavendra, S. *Tetrahedron Lett.* **2002**, *43*, 5105; (c) Yadav, J. S.; Reddy, B. V. S.; Kumar, G. M.; Murthy, Ch. V. S. R. *Tetrahedron Lett.* **2001**, *42*, 89.

10. *General procedure*: A mixture of 2,3-dihydro-4*H*-pyran-4-one[11] (1 mmol), aryl hydrazine (1.2 mmol) and montmorillonite KSF clay (1.0 g) in ethanol (10 mL) was stirred at reflux for the appropriate time (see Table 1). After complete conversion as indicated by TLC, the reaction mixture was filtered and washed with ethyl acetate (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford the corresponding optically active 5-substituted pyrazole in pure form. Compound **3a**: Liquid, $[\alpha]_D^{27}$ 31.8 (*c* 1.25, $CHCl_3$), IR (KBr): υ 3409, 3385, 3016, 2925, 1618, 1540, 1448, 1341, 1244, 1026, 867, 702 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.58–7.43 (m, 10H, aromatic), 7.40 (br s, 1H, NH), 7.30 (d, 1H, $J_{1,2} = 2.4$ Hz, H-1), 6.30 (d, 1H, $J_{1,2} = 2.4$ Hz, H-2), 4.62 (d, 1H, $J_{4,5} = 5.8$ Hz, H-4), 4.47 (s, 2H, –O*C*H$_2$–Ph), 4.39 (ABq, 2H, $J = 11.7$ Hz, –O*C*H$_2$–Ph), 4.15 (dt, 1H, $J_{4,5} = 5.8$, $J_{5,6} = 3.7$ Hz, H-5), 3.62 (m, 2H, H-6 and H-6′). ^{13}C NMR (75 MHz, proton decoupled): δ 145.0 (C-1), 130.1, 129.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 126.3, 126.0 (aromatic carbons), 104.8 (C-2), 74.7 (C-4), 73.4 (C-5), 72.4 and 71.1 (O*C*H$_2$–Ph), 70.8 (C-6), 29.5 (–*C*H$_2$–OBn). EIMS Mass: *m*/*z*: 339 (M^++1), 289, 269, 255, 241, 226, 181, 165, 154, 136, 123, 107. HRMS calcd for $C_{20}H_{22}N_2O_3$: 338.1630. Found: 338.1673. Compound **3b**: Liquid, $[\alpha]_D^{27}$ 39.1 (*c* 0.3, $CHCl_3$), IR (KBr): υ 3418, 3015, 2925, 1636, 1598, 1499, 1389, 1217, 1026, 867, 756 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, 1H, $J_{1,2} = 2.4$ Hz, H-1), 7.60–7.20 (m, 15H, aromatic protons), 6.58 (d, 1H, $J_{1,2} = 2.4$ Hz, H-2), 4.66 (d, 1H, $J_{4,5} = 7.5$ Hz, H-4), 4.47 (s, 2H, –O*C*H$_2$–Ph), 4.42 (ABq, 2H, $J = 11.7$ Hz, –O*C*H$_2$–Ph), 4.06 (dt, 1H, $J_{4,5} = 7.5$, $J_{5,6} = 3.8$ Hz, H-5), 3.68 (dd, 1H, $J_{6,6'} = 9.8$, $J_{5,6'} = 5.8$ Hz, H-6′), 3.58 (dd, 1H, $J_{6,6'} = 9.8$, $J_{6,5} = 3.8$ Hz, H-6). ^1C NMR (75 MHz, proton decoupled): δ 140.2 (C-1), 131.9, 130.2, 129.4, 129.0, 128.8, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.0, 126.4, 126.2, 126.0 (aromatic carbons), 106.1 (C-2), 73.3 (C-4), 72.7 (C-5), 72.3 (C-6), 70.5 and 69.5 (O*C*H$_2$–Ph), 29.7 (–*C*H$_2$–OBn). FAB Mass: *m*/*z*: 415 (M^++1), 307, 277, 173, 133, 91, 69, 55. HRMS calcd for $C_{26}H_{26}N_2O_3$: 414.1943. Found: 414.1901. Compound **3c**: Liquid, $[\alpha]_D^{27}$ 35.7 (*c* 0.7, $CHCl_3$); IR (KBr): υ 3443, 3032, 2868, 1594, 1489, 1389, 1214, 1091, 749 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, 1H, $J_{1,2} = 2.4$ Hz, H-1), 7.63–7.20 (m, 13H, aromatic), 6.55 (d, 1H, $J_{1,2} = 2.4$ Hz, H-2), 4.68 (d, 1H, $J_{4,5} = 6.3$ Hz, H-4), 4.54 (s, 2H, –O*C*H$_2$–Ph), 4.51 (Abq, 2H, $J = 11.7$ Hz, –O*C*H$_2$–Ph), 4.15 (m, 1H, H-5), 3.77 (dd, 1H, $J_{6,6'} = 9.8$, $J_{6,5} = 3.9$ Hz, H-6), 3.65 (dd, 1H, $J_{6,6'} = 9.7$, $J_{5,6'} = 5.8$ Hz, H-6′). ^{13}C NMR (75 MHz, proton decoupled): δ 152.0 (C-1), 134.2, 133.9, 132.3, 132.0, 131.5, 128.9, 128.8, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 127.0, 126.4, 126.0, 125.9, (aromatic carbons), 106.2 (C-2), 75.7 (C-4), 73.3 (C-5), 72.4 and 71.1 (O*C*H$_2$–Ph), 70.6 (C-6), 29.6 (*C*H$_2$–OBn). FAB Mass: *m*/*z*: 484 (M^++2), 467, 439, 415, 375, 345, 331, 289, 269, 255, 241, 226, 181, 165, 154, 136, 123, 107. HRMS calcd for $C_{26}H_{24}Cl_2N_2O_3$: 482.1163. Found: 482.1121. Compound **4**: Liquid, $[\alpha]_D^{27}$ 37.0 (*c* 0.75, $CHCl_3$), IR (KBr): υ 3030, 2922, 1742, 1587, 1479, 1371, 1235, 1096, 738 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, 1H, $J_{1,2} = 2.4$ Hz, H-1), 7.63–7.20 (m, 13H, aromatic), 6.51 (d, 1H, $J_{1,2} = 2.4$ Hz, H-2), 5.52 (dt, 1H, $J_{4,5} = 6.3$, $J_{5,6} = 3.8$ Hz, H-5), 4.83 (d, 1H, $J_{4,5} = 6.3$ Hz, H-4), 4.51 (s, 2H, CH_2–OBn), 4.50 (Abq, 2H, $J = 11.7$ Hz, CH_2–OBn), 3.81 (dd, 1H, $J_{6,6'} = 9.8$, $J_{5,6'} = 5.8$ Hz, H-6′), 3.77 (dd, 1H, $J_{6,6'} = 9.8$, $J_{6,5} = 3.8$ Hz, H-6), 2.07 (s, 3H, CH_3). ^{13}C NMR (proton decoupled): δ 170.1 (C–OAc), 134.2, 134.1, 134.0, 133.9, 133.0, 132.6, 132.3, 131.6, 129.9, 129.2, 129.0, 128.7, 128.5, 128.0, 127.5, 126.5, 126.3, 126.0 (aromatic carbons), 106.0 (C-2), 74.0 (C-4), 73.3 (C-5), 71.0 and 70.5 (–O*C*H$_2$–Ph), 68.5 (C-6), 21.0 (–*C*H$_3$–OAc). FAB Mass: *m*/*z*: 526 (M^++2), 245, 117, 43. HRMS calcd for $C_{28}H_{26}Cl_2N_2O_4$: 524.1269. Found: 524.1297. Compound **3d**: Brown liquid, $[\alpha]_D^{27}$ 22.5 (*c* 1.0, $CHCl_3$), IR (KBr): υ 3457, 3030, 2923, 1521, 1496, 1454, 1389, 1212, 1092, 760 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, 1H, $J_{1,2} = 2.3$ Hz, H-1), 7.60–7.20 (m, 14H, aromatic), 6.51 (d, 1H, $J_{1,2} = 2.3$ Hz, H-2), 4.70 (d, 1H, $J_{4,5} = 6.3$ Hz, H-4), 4.51 (s, 2H, –O*C*H$_2$–Ph), 4.53 (ABq, 2H, $J = 11.7$ Hz, –O*C*H$_2$–Ph), 4.23 (dt, 1H, $J_{4,5} = 6.2$, $J_{5,6} = 3.7$ Hz, H-5), 3.67 (dd, 1H, $J_{6,6'} = 9.8$, $J_{5,6'} = 5.8$ Hz, H-6′), 3.61 (dd, 1H, $J_{6,6'} = 9.8$, $J_{6,5} = 3.8$ Hz, H-6), 2.57 (q, 2H, $J = 7.6$ Hz), 1.07 (t, 3H, $J = 7.6$ Hz). ^{13}C NMR (proton decoupled): δ 143.4, (C-1), 134.1, 134.0, 133.9, 133.5, 133.1, 132.0, 129.8, 129.1, 128.8, 128.5, 128.0, 127.9, 127.6, 127.5, 126.7, 126.4, 126.2, 126.0, 125.8. (aromatic carbons), 105.3 (C-2), 75.7 (C-4), 73.3 (C-5), 71.0 and 69.5 (–O*C*H$_2$–Ph), 72.6 (C-6), 24.3 (–*C*H$_2$),14.8 (–*C*H$_3$). FAB Mass: *m*/*z*: 444 (M^++2), 382, 336, 292, 216, 202, 154, 121, 109, 91, 55. HRMS calcd for $C_{28}H_{30}N_2O_3$: 442.2256. Found: 442.2219.

11. The starting 2-formyl glycals were prepared according to the procedure reported in the literature: Kirschning, A. *J. Org. Chem.* **1995**, *60*, 1228–1232.