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Tetrahedron Letters 45 (2004) 3673–3676

Tetrahedron Letters

Montmorillonite clay catalyzed alkylation of pyrroles and indoles with cyclic hemi-acetals

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Received 14 November 2003; revised 27 February 2004; accepted 5 March 2004

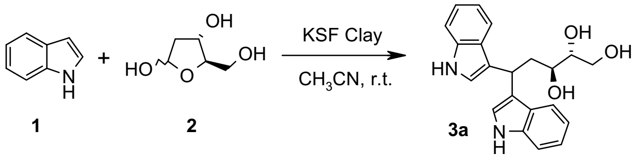
Abstract—Cyclic hemiacetals such as 2-deoxy-D-ribose and 2-deoxy-D-glucose react smoothly with pyrroles and indoles on the surface of montmorillonite KSF clay under extremely mild reaction conditions to afford optically active di-pyrrolyl and bis-indolyl alkanols in good yields with high selectivity.

Dipyrrolyl alkanols are important building blocks for the synthesis of *meso*-substituted porphyrins, porphyrinoid macrocycles and expanded porphyrins.[1] Particularly, optically active dipyrrolylmethanes are useful intermediates for the preparation of chiral porphyrins.[2] The simplest and most straightforward method for the synthesis of dipyrrolylmethanes involves the acid catalyzed condensation of aldehydes with pyrrole,[3] wherein the suppression of polymerization is achieved by using a large excess of pyrrole without any solvent.[4] The preparation of dipyrrolylmethanes is usually associated with the formation of tripyrromethanes as minor products.[5] Since dipyrrolyl alkanols have become increasingly useful and important in the synthesis of chiral porphyrins,[6] the development of simple, convenient and environmentally benign approaches are desirable.

Recently, the use of solid acids such as clays, zeolites and ion-exchange resins has achieved importance in organic chemistry.[7] 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.[8] 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.[9] However, there is no precedent for the synthesis of optically active dipyrrolyl alkanols from sugar hemi-acetals and pyrrole.

In continuation of our research programme on the use of clays for organic transformations,[10] we report herein a novel method for the synthesis of dipyrrolyl and bis-indolyl-alkanols using inexpensive montmorillonite clay as a reusable solid acid catalyst. Thus treatment of indole **1** with 2-deoxyribose **2** in the presence of montmorillonite KSF clay afforded the optically active 5,5-di(3-indolyl)-(2*R*,3*S*)-pentane-1,2,3-triol **3a** in 80% yield (Scheme 1).

Several substituted indoles such as 2-methyl-, 5-methoxy-, 7-ethyl-, *N*-benzyl- and 5-bromo-indoles reacted smoothly with 2-deoxyribose to give the corresponding bis-indolyl alkanols **3** in good yields (Table 1, entries b–f). Similarly, pyrrole and *N*-methylpyrrole afforded the respective optically active dipyrrolyl alkanols in good yields (Table 1, entries g–h, Scheme 2).



Scheme 1.

Keywords: Solid acids; Hemi-acetals; Alkylation; Heteroaromatics.

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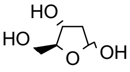
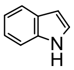
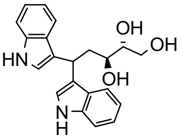
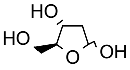
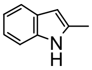
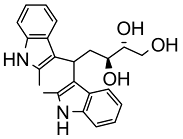
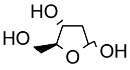
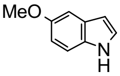
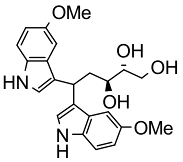
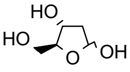
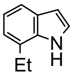
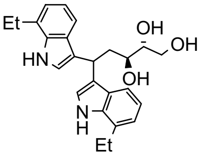
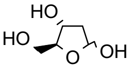
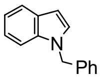
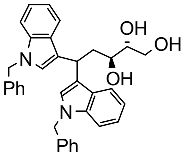
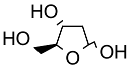
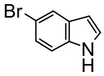
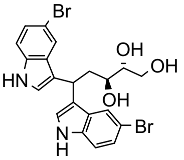
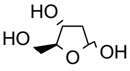
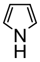
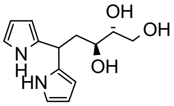
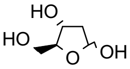
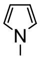
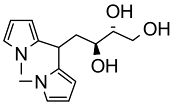
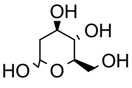
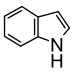
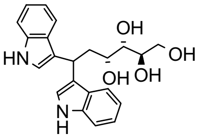
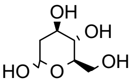
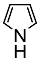
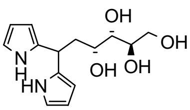
doi:10.1016/j.tetlet.2004.03.039

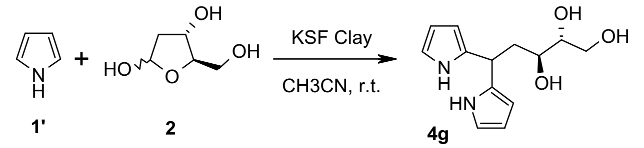
Table 1. KSF clay-promoted synthesis of chiral dipyrrolyl or bis-indolyl derivatives

Entry	Hemi-acetal	Pyrrole/indole	Product[a]		Yield (%)[b]	Time (h)
a				**3a**	80	4.0
b				**3b**	85	5.5
c				**3c**	82	5.0
d				**3d**	79	5.5
e				**3e**	75	6.0
f				**3f**	70	5.5
g				**4g**	62	4.5
h				**4h**	58	5.0
i				**5i**	70	6.0
j				**6j**	60	7.0

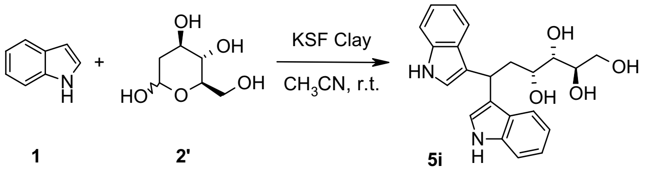
[a] All the products were characterized by ^{1}H NMR, IR and mass spectroscopy.

[b] Isolated and unoptimized yields.

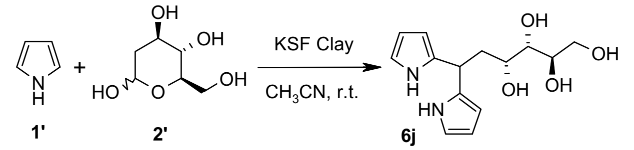
Interestingly, treatment of 2-deoxy-D-glucose with indole in the presence of montmorillonite clay afforded 6,6-di(3-indolyl)-(2*R*,3*S*,4*R*)-hexane-1,2,3,4-tetraol in 70% yield (Table 1, entry i, Scheme 3).



Scheme 2.



Scheme 3.



Scheme 4.

Similarly, pyrrole also reacted smoothly with 2-deoxy-D-glucose to give the corresponding 6,6-di(2-pyrrolyl)-(2*R*,3*S*,4*R*)-hexane-1,2,3,4-tetraol in 62% yield (Table 1, entry j, Scheme 4).

These reactions probably proceed through formation of a 2-tetrahydro-2-furanyl-1*H*-pyrrole followed by cleavage of the tetrahydrofuran ring and subsequent addition of another molecule of pyrrole leading to the dipyrrolyl alkanols (Scheme 5).

In the absence of the clay, no reaction was observed between a sugar hemi-acetal and pyrrole or indole. In all cases, the reactions proceeded smoothly at ambient temperature with high selectivity. No tripyrrolyl derivatives were obtained under reaction conditions. Among several 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. For example, treatment of indole with 2-deoxy-D-ribose for 4 h in the presence of KSF clay or 10 mol% InBr$_3$ or Sc(OTf)$_3$ or Yb-(OTf)$_3$·H$_2$O afforded 80%, 65%, 50% and 35% yields, respectively. Furthermore, pyrrole underwent partial polymerization in the presence of metal triflates. Pyrrole was also not compatible with conventional Lewis acids such as aluminium chloride or boron trifluoride etherate. This is because of the sensitivity of pyrrole to strongly acidic conditions. Although, this reaction proceeds smoothly in commercial grade acetonitrile (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 indoles and pyrroles and the results are presented in Table 1.[11]

In conclusion, we describe a novel and efficient protocol for the synthesis of sugar derived optically active dipyrrolyl and bis-indolyl alkanols from 2-deoxy-D-ribose and indoles and pyrroles using the inexpensive and readily available solid acid, montmorillonite KSF clay.

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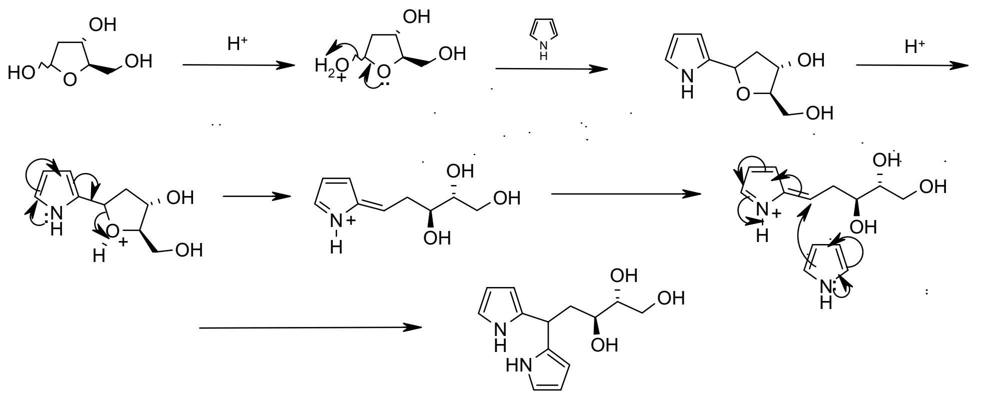

Scheme 5.

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11. General procedure: A mixture of 2-deoxy-D-ribose or 2-deoxy-D-glucose (1 mmol) and, indole (2 mmol) or pyrrole (4 mmol) montmorillonite KSF (1.0 g) in acetonitrile (10 mL) was stirred at room temperature for the time required to complete the reaction (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 bis-indolyl or dipyrrolyl alkanol in pure form. Compound **3a**: Solid, mp 146–147 °C $[\alpha]_D^{27}$ −13.0 (c 1.0, EtOH), IR (KBr): v 3409, 3286, 2925, 1698, 1618, 1540, 1448, 1341, 1244, 1026, 867, 702 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.10–2.25 (m, 1H), 2.45–2.60 (m, 1H), 3.35–3.65 (m, 4H), 4.80 (d, $J = 6.5$ Hz, 1H), 6.90 (dt, $J = 7.7$, 0.7 Hz, 2H), 7.05 (dt, $J = 7.9$, 0.8 Hz, 2H), 7.10 (d, $J = 1.7$ Hz, 2H), 7.28 (dd, $J = 7.9$, 0.7 Hz, 2H), 7.60 (dd, $J = 7.7$, 0.8 Hz, 2H), 9.80 (br s, NH, 1H), 9.90 (br s, NH, 1H). EIMS mass: m/z: 350 M$^+$, 245, 117, 43. Compound **4g**: Brown liquid, $[\alpha]_D^{27}$ 3.5 (c 1.0, EtOH), IR (KBr): v 3444, 2970, 1235, 1187, 1015, 753 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.95–2.0 (m, 1H), 2.05–2.25 (m, 1H), 3.40–3.80 (m, 4H), 4.30 (d, $J = 6.2$ Hz, 1H), 5.80 (dd, $J = 2.0$, 2.5 Hz, 2H), 5.98 (d, $J = 2.0$ Hz, 2H), 6.58 (d, $J = 2.5$ Hz, 2H), 9.20 (br s, NH, 1H), 9.50 (br s, NH, 1H). FAB mass: m/z: 250 M$^+$, 155, 98, 69, 55. Compound **5i**: Viscous liquid, $[\alpha]_D^{27}$ 12.5 (c 0.6, EtOH), IR (KBr): v 3435, 3278, 2925, 1700, 1646, 1516, 1457, 1277, 1222, 1092, 1031, 746 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.25–2.40 (m, 2H), 3.20–3.39 (m, 2H), 3.45–3.60 (m, 3H), 3.70–3.80 (br s, OH, 1H), 3.85–4.05 (br s, OH, 2H), 4.20–4.25 (br s, OH, 1H), 4.78 (d, $J = 6.2$ Hz, 1H), 6.85 (dt, $J = 7.6$, 0.7 Hz, 2H), 7.05 (dt, $J = 7.9$, 0.8 Hz, 2H), 7.10 (d, $J = 1.8$ Hz, 2H), 7.30 (dd, $J = 7.9$, 0.7 Hz, 2H), 7.58 (t, $J = 7.6$, 0.8 Hz, 2H), 10.2 (br s, NH, 1H), 10.3 (br s, NH, 1H). FAB mass: m/z: 380 M$^+$, 259, 245, 176, 154, 137, 107, 95, 81, 69, 57, 43.