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MONTMORILLONITE: A MILD AND EFFICIENT RECYCLABLE SOLID ACID CATALYST FOR DETRITYLATION OF TRITYL TETRAZOLE IN SARTAN MOLECULES

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ABSTRACT

Proton and metal ion-exchanged Montmorillonite catalyzes the detritylation of trityl tetrazole in sartan molecules under mild conditions in high yields. The reactions are carried out in methanol in presence of 1 equivalents of water. Catalyst was reusable without any appreciable loss in its catalytic activity.

KEY WORDS : detritylation montmorillonite sartan molecules.

1. INTRODUCTION

Trityl and related groups have been used extensively for N- and O-protection, where detritylation is accomplished employing acidic conditions either with protonic acids (e.g.HCl, CF_3CO_2H, CCl_3CO_2H) or Lewis acids (e.g.$ZnBr_2$, diisopropylaluminum chloride, Yb $(OTf)_3$)[1-12]. Other methods reported for removal of trityl groups involve reductive protocols (e.g. Li powder and a catalytic amount of naphthalene).[13] Many manufacturing reactions for fine chemicals and pharmaceuticals rely on homogeneous Lewis acid catalysts. However above methods have associated drawbacks, such as long reaction times, use of hazardous reagents and the inability to recycle. In recent years, heterogeneous catalysts have gained significant importance from environmental and economical stand points, recently reported two methods in this era were silica absorbed sulfuric acid [14] and silica gel supported ceric ammonium nitrate [15] for detritylation. The use of clays as catalysts and catalyst supported has received considerable attention recently [16,17].Herein, we report a environmental and economical benign deprotection of trityl group in trityl tetrazole sartan molecules by proton and metal ion-exchanged montmorillonite, a heterogeneous solid acid catalyst which is reusable and

recyclable. Sartans are a class of drugs that are effective in treating hypertension and heart failure. These drugs block the rennin angiotension system and represent one of the most therapeutic interventions available for the treatment of hypertension [18-20]. There are about seven sartans in clinical practice, of which five of them possess a tetrazole moiety in their structure. The protection and de protection of the N-atom of the tetrazole moiety becomes essential during the synthesis of the sartan drugs.

Montmorillonites, referred to as monts, are hydrophilic clays with a layered structure. They are of considerable interest as environmentally benign and reusable catalysts. Owing to their ion-exchange properties, various types of metal cations can be introduced readily into their expansible interlayer spaces.[21,22] The mont lattice is composed of a sheet of gibbsite ($Al_2(OH)_6$) Sand witched between two sheets of tetrahedrally co-ordinated silicate $(SiO_4)^{-4}$-sheets.

The three sheet layer repeats itself and the interlayer space holds the key to the chemical and physical properties of the clay. An important and useful properties of mont stems from its high degree of efficiency for M^+ cation exchange.[23] The various metal cations are successfully introduced within the interlayer's via a simple ion-exchange method to afford metal ion species in unique structures as efficient solid acid catalysts.[24]

Acidic character of clay [25]

The detritylation carried out using clay catalysts due to acidic character of clay, which may function as bronsted or Lewis acid or both. The Lewis acidity due to Al^{+3} and Fe^{+3} at the crystal edges and their activities may be further tuned by metal ion exchange with the introduction of large no. of Lewis acidic sites.

The bronsted acid character of clays arises mainly due to the dissociation of the intercalated water molecules co-ordinated to cations.

$$[M(H_2O)n]^{3+} \rightleftharpoons [M(H_2O)n\text{-}1(OH)]^{2+} + H^+$$

RESULTS AND DISCUSSION

At first, we evaluated the feasibility of the reaction with detritylation of [2-(N-Triphenyl methyl tetrazolyl)-4'-bromo methyl biphenyl (TTBB) (1mmol) using H-mont (10mol%) in methanol at ambient temperature to afford the corresponding detritylated product as a model reaction. We studied different reaction parameters.

In the first experiment, the effect of different amounts of monts on the efficiency of the model reaction in methanol was studied. It was found that 1 mmol(10mol%) of mont was an appropriate amount for catalyzing the reaction.Using further amounts of monts had no distinguishable effect on the efficiency of the model reaction. The choice of solvent was also important, the different solvents such as MeOH, MeCN, CH_2Cl_2, EtOAc, THF, CH_3COCH_3 were used in the reaction and among them MeOH was the most efficient (Table1)

Table1. Effect of solvent on the detritylation of TTBB (1 mmol) with a catalytic amount of Mont (0.55g, 10mol%)

Entry	Solvent	Yield[a](%)
1	MeOH	98
2	MeCN	75
3	CH_2Cl_2	65
4	EtOAc	70
5	THF	65
6	CH_3COCH_3	55

[a]isolated yield

The temperature of the reaction was also much considerable effect on the model reaction. At room temperature the reaction was not completed even after stirring for 1day, at 45^0C the reaction leads to completion in 5 hours. 1eq. of water was also added to enhance the rate of reaction. We screened various metal exchanged monts (K-10 mont, Ti-mont, Cu-mont, Al-mont, Fe-mont, Sn-mont ,Zn-mont, Ni-mont, Sc-mont,,Ce mont etc.) and product obtained in excellent yields (Table2).

Table 2. Deprotection of TTBB catalyzed by H^+ and M^{+n}-montmorrillonites [a]

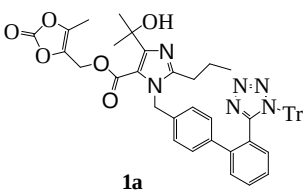
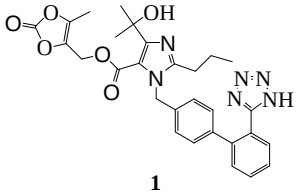
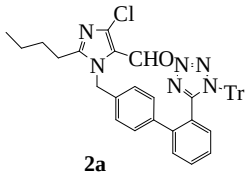
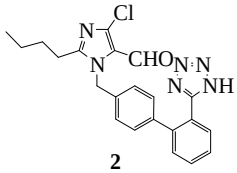
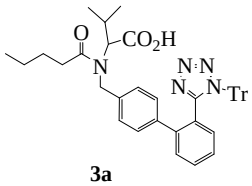
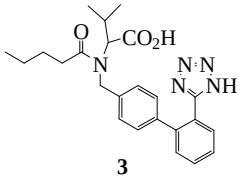
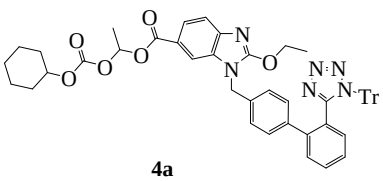
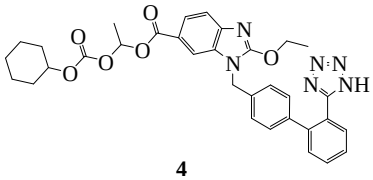
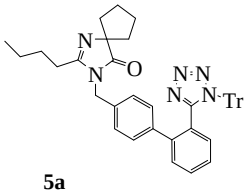
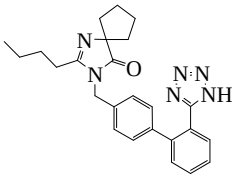
Entry	Catalyst	Yield (%)
1	K 10-mont	76
2	H^+-mont	98, 95[b]
3	Ti^{+4}-mont	98,95[b]
4	Zn^{+2}-mont	91
5	Al^{+3}-mont	82
6	Cu^{+2}-mont	92
7	Fe^{+3}-mont	92
8	Sn^{+4}-mont	90
9	Ce^{+4}-mont	96
10	Na^+-mont	60
11	Bentonite	82

[a] TTBB(1mmol), catalyst(0.05g) in methanol were stirred at 45^0c about 4-5 h

[b] Isolated yield after fifth cycle

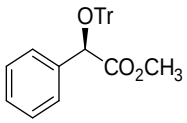
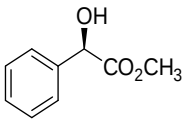
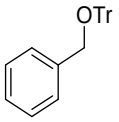
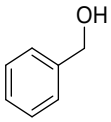
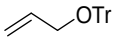
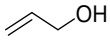
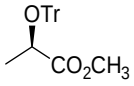
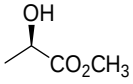
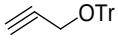
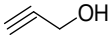
After establishing optimal reaction conditions, which prompted us to screen all the tetrazole containing sartan drugs. N-Tritylated olmesartan medoxmil, losartan aldehyde, valsartan, candesartan cilexitil and irbesartan were synthesized and subjected to N-deprotection using various M^{+n}- monts and the results obtained are shown in table 3.

Table 3. N- detritylation of sartan molecules by H^+ and M^{+n} montmorillonite

Entry	Reactant	Product	Yield(%)
1	 **1a**	 **1**	>90
2	 **2a**	 **2**	>92
3	 **3a**	 **3**	>94
4	 **4a**	 **4**	>91
5	 **5a**	 **5**	>94

The reaction times around 4-5 hours at 45^0C and the products were isolated without any side reactions in 90-95% yield The mont catalyst could be reused for several cycles with consistent activity after activation at 120^0C for 1 h; there was a slight decrease in activity after the fifth use in the reaction forming. To investigate the generality and versatility of this method, the reaction was extended to O-detritylation.using the optimized reaction conditions, the deprotection of trityl ether of R-(-) methyl mandelate was examined and the corresponding detritylated product was obtained in excellent yield (table 4). Further application to other heterocyclic trityl amines remains to be exploited.

Table 4. O- detritylation H^+ and M^{+n} montmorillonite

Entry	Reactant	Product	Yield(%)
1			>93
2			>95
3			>96
4			>95
5			>97
6			>87

Experimental Section

Preparation of H^+-Mont Catalyst

To a stirred solution of K-10 Montmorillonite (10 gr) in DM water (100 ml) concentrated sulphuric acid (7.5 ml) is added at room temperature. The mixture was stirred at 80°C for 24 hours. The reaction mixture was filtered on a suction funnel washed with deionized water (6x200 ml) until SO_4^{-2} ion free (as tested by $BaCl_2$). The collected clay was dried at 100°C for 6 hours to give H^+-Mont as an off-white solid (8 g).

A Typical Procedure for Preparation of metal ion-Exchanged Mont Catalyst

M^{+n} mont (M= Al, Ga, Sc, Ti, Zr, Ni, Cu, Zn, Fe, Sn, Ce, La, Sm) were prepared from Na-Mont (cation-exchange capacity = 1.19 mequiv g^{-1}) by cation-exchange using aqueous solutions of corresponding salts, such as $Al(NO_3)_3.9H_2O$, $Sc(NO_3)_3.4H_2O$, $Ti(Oi\text{-}Pr)_4$, $Fe(NO_3)_3.9H_2O$, $Ni\text{-}(NO_3)_2.6H_2O$, $Cu(NO_3)_2.3H_2O$, $Zn(NO_3)2.6H_2O$, $Ga(NO_3)_3.8H_2O$, $ZrCl_4$, $SnCl_4.5H_2O$, $La(NO_3)_3.6H_2O$ and $Sm(NO_3)_3.6H_2O$. A typical procedure is described below.

To a solution of $Al(NO_3)_3.9H_2O$ (100 g, 0.26 mol) in deionized water (800ml) was added Na-Mont (cation-exchange capacity = 1.19 mequiv g^{-1}) (100 g) . The mixture was stirred vigorously at room temperature for 16 hours. The resultant suspension was filtered on a Buchner funnel by suction. The clay was collected suspended again in deionized water (400 ml) with stirring at room temperature for 15 hours, filtered on a suction funnel, and washed with deionized water (200 ml). The precipitate was again suspended in deionized water (400 ml) with stirring at room temperature for 14 hours, filtered on a suction funnel, and washed with deionized water (200 ml). The precipitate was suspended again in a mixture of deionized water (200 ml) and methanol (200 ml) with stirring at room temperature for 8 hours and filtered. The collected clay was dried at 100°C for 6 hours and ground to pass through a 60 mesh screen. The powdery clay was dried at vaccum at 100°C for 4 hous to give Al-Mont as an off-white solid (89 g).

General Procedure for the detritylation of sartan molecules

H-Mont (0.1 g) was added to a suspension of compound 1a (1 g, 1.25 mmol) in methanol at room temperature and stirred at 40°C about 4 hours. The completion of the reaction was monitored by TLC, after completion of reaction catalyst is separated by simple filtration, washed with methanol and reused for several cycles. The reaction was cooled to 25°C until trityl methyl ether crystallized, separate it by filtration then filtrate methanol was evaporated in vaccuo to give compound 1 in 95% yield.

Compound 1a

^{1}H NMR(300 MHz,$CDCl_3$) δ 0.91(t, 3H, CH_3), 0.62 (t, 6H, CH_3), 1.68(t, 2H, CH_2), 2.18 (s, 3H, CH_3), 2.54 (t, 2H, CH_2), 4.96 (NCH_2), 5.40 (s, 2H, OCH_2), 6.67 (d, 2H, J=8.6Hz, ArH), 6.95 (d, 6H, J=8Hz, ArH), 7.07 (d, 2H, J= 8.6Hz, ArH), 7.24-7.54 (m, 11H, ArH) ,7.8 (d, 1H J=8.3Hz, ArH) ; MS (ESI): M= 800, found 801 $[M+H]^+$.

Compound 1

Mp: 175-179^o C; ^{1}H NMR(300 MHz, $CDCl_3$) δ 0.91(t, 3H, CH_3), 1.62 (t, 6H, CH_3), 1.68 (t, 2H, CH_2), 2.18 (s, 3H, CH_3), 2.54 (t, 2H, CH_2), 4.96 (NCH_2), 5.40 (s, 2H, OCH_2), 6.77 (d, 2H, J=8.6Hz ArH) ,7.06 (d, 2H, J=8.6Hz ,ArH), 7.42-7.62 (m, 3H, ArH), 7.80 (d, 1H ,J=8.3Hz, ArH); ^{13}C NMR(200 MHz, $CDCl_3$); δ 13.7, 16.2, 24.1, 31.3, 32.7, 48.4, 62.7, 74.2, 116.2, 121.8, 127.8, 128.0, 128.2, 128.4, 129.3, 129.5, 133.4, 135.1, 135.4, 144.2, 147.5, 152.4, 163.5, 167.9; MS (ESI): M=558, found 559 $[M+H]^+$.

Compound 2a

Mp: 175-179^o C; ^{1}HNMR (400 MHz, $CDCl_3$): δ 0.86 (t, 3H, CH_3), 1.24-1.33 (m, 2H, CH_2), 1.60-1.67 (m, 2H ,CH_2) , 2.52 (m, 2H, CH_2), 5.44 (s, H, CH_2), 6.82 (d, 2H, J=8Hz, ArH), 6.90 (d, 6H, J=7.4Hz , ArH), 7.08 (d, 2H, J=8.6Hz ,ArH), 7.23-7.27 (m, 6H, ArH), 7.32(t, 4H, ArH), 7.43-7.50(m,2H, ArH), 7.91-7.93 (dd, H, J=5.7Hz , ArH), 9.73 (s, 1H, CHO); MS (ESI): M= 662, found 663 $[M+H]^+$.

Compound 2

^{1}HNMR (400MHz, $CDCl_3$):δ 0.86 (t, 3H, CH_3), 1.24-1.33 (m, 2H, CH_2), 1.60-1.67 (m, 2H, CH_2) ,2.52 (m, 2H, CH_2), 5.25 (s, 2H, CH_2), 7.12 (d, 2H, J=8Hz, ArH), 7.28-7.33 (m, 3H, ArH), 7.40-7.49 (m, 3H, ArH), 9.73 (s, 1H, CHO); ^{13}C NMR(200 MHz, $CDCl_3$); δ 13.51, 22.18, 29.04, 47.74, 110.05, 118.36, 124.11, 126.59, 127.65, 129.16, 129.81, 132.76, 133.61, 136.01, 137.69, 149.33, 154.46, 181.73; MS (ESI): M= 420, found 421 $[M+H]^+$.

Compound 3a

^{1}HNMR (400MHz, DMSO-d_6): δ 0.80-0.95 (m, 9H, CH_3, CH_2), 1.25 (d, 2H, CH_3), 2.24-2.40 (m, H, CH), 4.41-4.50 (m, H, CH), 4.61 (s, 2H, CH_2), 6.88-7.50 (m, 23H, ArH); MS (ESI): M= 677, found 676 $[M-H]^+$.

Compound 3

Mp: 116-117^{o} C; ^{1}HNMR (400MHz, $CDCl_3$): δ 0.80-0.95 (m, 9H, CH_3, CH_2), 1.25 (d, 2H, CH_3), 2.24-2.40 (m, H, CH), 4.41-4.50 (m, H, CH), 4.61 (s, 2H, CH_2), 7.10 (t,2 H, ArH), 7.20 (d, 2H, J=8Hz, ArH), 7.51-7.62 (m, 2H, ArH), 7.64-7.69 (m, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.2, 20.06, 22.2, 27.3, 28.05, 32.9, 49.9, 63.4, 70.03, 126.7, 127.4, 128.2, 128.8, 129.3, 131.0, 131.1, 131.54, 138.2, 141.7, 171.8, 172.4, 174.0; MS (ESI): M= 435, found 434 $[M-H]^+$.

Compound 4a

^{1}H NMR (300 MHz,$CDCl_3$): δ 1.88-1.14 (m, 16H), 4.55-4.43 (m,3H), 5.63 (dd, 2H, J=27.1 Hz), 6.73 (m,1H), 6.84 (d, H, J=7.4Hz), 6.94 (d, 2H, J=7.8Hz), 7.0 (t, 1H. J=7.6 Hz), 7.26 (d,1 H. J=7.6 Hz), 7.35-7.31(m, 1H), 7.58-7.56 (m, 3H), 8.0 (d, 1H, J=8.2 Hz); MS (ESI): M=841, found 842 $[M+H]^+$.

Compound 4

Mp: 157-160^{o} C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.88-1.14 (m, 16H), 4.55-4.43 (m,3H), 5.63 (dd, 2H, J=27.1Hz), 6.73 (m,1H), 6.84 (d, 2H, J=7.4Hz), 6.94 (d, 2H, J=7.8Hz), 7.0 (t, 1H. J=7.6Hz), 7.26 (d, 1H. J=7.6Hz), 7.35-7.31 (m,1H), 7.58-7.56 (m, 3H), 8.0 (d, 1H, J=8.2Hz); ^{13}C NMR(75 MHz,$CDCl_3$): δ 14.4, 19.0, 23.4, 24.9, 31.2, 46.7, 67.7, 77.6, 91.7, 115.3, 120.6, 121.2, 122.3, 124.1, 124.9, 128.2, 129.4, 130.2, 130.4, 131.1, 136.1, 138.0, 139.5, 140.8, 152.2, 154.7, 157.7, 163.1; MS (ESI): M=598, found 599 $[M+H]^+$.

Compound 5a

^{1}HNMR (400MHz, $CDCl_3$): δ 0.83 (t, 3H, CH_3), 1.29 (m, 2H, CH), 1.54 (m, 2H, CH), 1.81 (d, 2H, CH), 2.01 (t, 6H, CH_2), 2.23 (t, 2H, CH), 4.57 (t,2H, CH_2), 6.92 (d, 8H, J=7.9Hz, ArH), 7.10 (d, 2H, J=8Hz, ArH), 7.24-7.35 (m, 11H, ArH), 7.45-7.48 (m, 2H, ArH); MS (ESI): M= 670, found 671 $[M+H]^+$.

Compound 5

Mp: 165-168^{o} C; ^{1}HNMR (400MHz, $CDCl_3$); δ 0.83 (t, 3H, CH_3), 1.29 (m, 2H, CH),1.54 (m, 2H, CH), 1.81 (d, 2H, CH), 2.01 (t, 6H, CH_2), 2.23 (t, 2H, CH), 4.57 (t, 2H, CH_2), 7.12(d, 2H, J=8Hz ,ArH), 7.28-7.33 (m, 3H, ArH), 7.40-7.49 (m, 3H, ArH); MS (ESI); ^{13}C NMR(300 MHz, $CDCl_3$); δ 14.0, 19.0, 26.1, 29.8, 37.6, 44.2, 72.7, 124.4, 127.7, 128.8, 130.2, 131.4, 131.5, 131.9, 134.9, 139.9, 141.8, 155.9, 172.5, 180.4; MS (ESI): M=428, found 429 $[M+H]^+$.

CONCLUSION

In summary, we have demonstrated a simple, efficient, and green protocol for N-detritylation and O-detritylation in sartan molecules by using monts as solid acid catalysts under mild conditions. The method offers several advantages such as mild conditions, high yields of products, operational simplicity, inexpensive recyclable and the use of an environmentally friendly green Lewis acid catalyst. This should be a useful addition to synthetic methodology and valuable information to the process chemistry for multigram scale synthesis of sartan molecules.

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