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A combination of trimethylsilyl chloride and hydrous natural montmorillonite clay: an efficient solid acid catalyst for the azidation of benzylic and allylic alcohols with trimethylsilyl azide†

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We present a new procedure to convert *in situ* natural montmorillonite clay into a partially acidified one using a catalytic amount of trimethylsilyl chloride and trace water. We demonstrate that the acidic montmorillonite can catalyze the direct azidation of various benzylic and allylic alcohols with trimethylsilyl azide.

Montmorillonite (Mont) is one of the abundant naturally-occurring clays. It is composed of stacked, negatively charged, two-dimensional aluminosilicate layers with exchangeable cationic species, mostly sodium ions, between the layers. Substitution of the sodium ions by protons or multivalent metal ions turns the natural montmorillonite (Na-Mont) into an acidic clay which can be employed as a catalyst for various organic transformations.[1] For example, proton-exchanged montmorillonite (H-Mont) was utilized for the alkylation of typical nucleophiles, such as amine and allyltrimethylsilane, with alcohols.[2] We also demonstrated the efficient catalysis of tin(IV)-montmorillonite (Sn-Mont)[3] for the reactions of various benzylic and allylic alcohols with typical nucleophiles, such as allytrimethylsilane,[4] malonates,[5] cyanotrimethylsilane[6] and triethylsilane.[7] These reactions are attributed to the strong acidity and the unique structural character of Sn-Mont; the alcohols first underwent protonation, followed by dehydration with Sn-Mont to form benzylic carbenium intermediates, which were trapped between the montmorillonite silicate layers. It is considered that the low nucleophilic montmorillonite silicate anions catalyzed the reaction not only by stabilizing the carbenium ions, but also by accelerating the reactions between the carbenium ions and the nucleophiles.

In contrast to conventional acid catalysts, such as $BF_3 \cdot Et_2O$ or $AlCl_3$, the solid acid montmorillonites tend to tolerate the presence of trace water in the reaction system, which in most cases, helps simplify the synthetic procedures for various acid-catalyzed reactions as well as has a significant advantage regarding their reuse.

Previously, we reported the chlorination of various benzylic and allylic alcohols using trimethylsilyl chloride (TMSCl) and hydrous natural Na-Mont,[8] which was comparable to the results obtained using the *intrinsically acidic* Sn-Mont or H-Mont. During this chlorination, TMSCl and trace water included in the Na-Mont generates hydrogen chloride, which is then trapped by the Na-Mont and promotes the generation of the corresponding carbenium ions from the alcohols through protonation and dehydration.[9,10] The subsequent reaction between the carbenium ions and the chloride ions then forms the chlorinated products. Since chloride ions have a relatively poor nucleophilicity, we postulate that if a more powerful nucleophile than a chloride ion coexists in the system, the carbenium ions will preferentially react with the more reactive nucleophile to afford the corresponding substituted products. If this is correct, the alcohols bearing poorly-leaving hydroxy groups can be directly substituted with preferred nucleophiles simply by mixing the natural Na-Mont, TMSCl and a nucleophile in a flask.

To confirm our hypothesis, we used benzhydrol **1a** as a model benzylic alcohol and trimethylsilyl azide ($TMSN_3$) as the nucleophile. $TMSN_3$ has previously been used with catalytic amounts of metal catalysts, such as $Fe(OTf)_3$,[11] magnetic nano Fe_3O_4,[12] and $InBr_3$,[13] as well as with $BF_3 \cdot Et_2O$,[14] for the direct azidation of alcohols. Our results are summarized in Table 1.

As we expected, when a mixture of **1a**, Na-Mont, 1 equiv. of $TMSN_3$, and 1 equiv. of TMSCl was stirred at room temperature (RT) for 40 min, the corresponding azide product **4a** was obtained in 79% yield (entry 5 of Table 1) together with benzhydryl chloride in 20% yield, as a result of the simultaneous chlorination and azidation of the intermediary carbenium ions. In the hope of suppressing the chlorination, the reaction was performed again under the same conditions except using a catalytic amount (6 mol%) of TMSCl. After 40 min, we were

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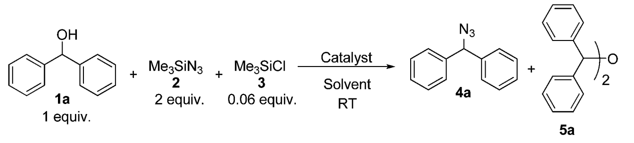
Table 1 Optimization of reaction conditions



Entry	Catalyst	Solvent	Reaction time	4a[a]	5a[a]
1	—	CH_2Cl_2	40 min	0%	0%
2[b]	$BF_3 \cdot Et_2O$	CH_2Cl_2	40 min	0%	0%
3[c]	Hydrous Na_2SO_4	CH_2Cl_2	40 min	0%	0%
4[d]	Na-Y	CH_2Cl_2	40 min	0%	0%
5[e]	Na-Mont	CH_2Cl_2	40 min	79%	0%
6	Na-Mont	CH_2Cl_2	40 min	99%	0%
7[f]	Na-Mont	CH_2Cl_2	40 min	98%	1%
8	H-Mont	CH_2Cl_2	40 min	99%	0%
9	Sn-Mont	CH_2Cl_2	40 min	99%	0%
10[g]	Na-Mont	CH_2Cl_2	40 min	3%	0%
11[h]	Na-Mont	CH_2Cl_2	40 min	0%	0%
12[i]	Na-Mont	CH_2Cl_2	40 min	94%	2%
13	Na-Mont	Hexane	40 min	98%	$\ll$1%
14	Na-Mont	Et_2O	40 min	54%	5%
15	Na-Mont	Acetone	40 min	0%	18%
16[j]	Na-Mont	CH_2Cl_2	10 min	93%	2%

[a] The ^{1}H-NMR yield based on mesitylene as the internal standard. [b] 8 mol% of $BF_3 \cdot Et_2O$ was employed. [c] Refer to ESI for details on the preparation of hydrous Na_2SO_4. [d] 50 mg of NaY was employed as the catalyst. [e] 1 equiv. of Me_3SiN_3 and 1 equiv. of TMSCl were employed. Benzhydryl chloride was obtained as a side product in 20% yield. [f] 0.06 equiv. of AcCl was used instead of TMSCl. [g] 0.003 equiv. of TMSCl was employed. [h] No TMSCl was used. [i] 1.5 equiv. of Me_3SiN_3 was employed. [j] A trace amount of **1a** remained.

surprised to find that **4a** was formed in 99% yield together with benzhydryl chloride in less than 0.1% yield (entry 6). When the reaction was performed with a catalytic amount (6 mol%) of acetyl chloride (AcCl), which also deliberated HCl upon contact with water, **4a** was formed in 98% yield together with **5a** in 1% yield (entry 7). No reaction proceeded when a combination of Na-Mont and $TMSN_3$ or that of TMSCl and $TMSN_3$ was applied (entries 1 and 11), concluding that the combination of Na-Mont, TMSCl, and $TMSN_3$ are essential to the successful azidation. When the amount of TMSCl was reduced from 6 mol% to 0.3 mol%, **4a** was only obtained in very low yield (entry 10), suggesting that the efficiency of the azidation significantly depends on the amount of TMSCl employed.

Surprisingly, when 8 mol% $BF_3 \cdot Et_2O$, a representative homogenous acid catalyst, was employed as a control catalyst, the formation of **4a** was not observed.[15] We also performed the reaction using typical acidic montmorillonites, such as H-Mont or Sn-Mont, as the acid catalysts. In each case, azide product **4a** was obtained in almost quantitative yield (entries 8 and 9). A survey of the solvent effects disclosed that undried CH_2Cl_2 (water content: <0.2%) was the solvent of choice (entries 6, 13–15).

By use of the optimized conditions shown in entry 6, the scope of benzylic and other alcohols as well as benzylic ethers was next investigated. The results are summarized in Fig. 1 and 2.

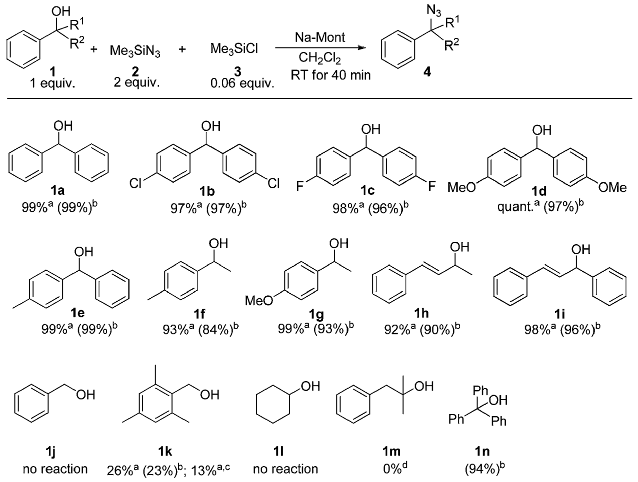
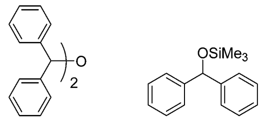


Fig. 1 Scope of substrates. (a) The ^{1}H-NMR yield based on mesitylene as the internal standard. Reaction conditions: 1 mmol of **1a**, 2 mmol of Me_3SiN_3, 0.06 mmol of TMSCl, 50 mg of Na-Mont and 5 mL of CH_2Cl_2. (b) In parentheses are the yields of products obtained after column chromatography. (c) The yield of the product obtained when 0.06 equiv. of AcCl was used instead of TMSCl. (d) Dehydration product was formed instead.

In general, the azidation method is applicable to various benzylic alcohols: benzhydrol **1a** underwent the azidation in almost quantitative yield. Benzylic alcohol **1b** bearing an electron-withdrawing chlorine, or those with electron-donating groups **1d** and **1e** gave the corresponding azides in almost quantitative yields. The azidation of benzylic alcohol **1c** having a fluorine atom was also successful. 1-Arylethanols, such as **1f** and **1g**, also underwent the azidation in excellent yields. This method is also applicable for the azidation of allylic alcohols, such as **1h** and **1i**, yielding azides **4h** and **4i** in 90% and 96% isolated yields, respectively. It should be noted that for azide **4h**, the azide ion is attached to the original position of the hydroxyl of **1h**, not at the benzylic site. We compared the difference in the Gibbs free energy (G) between **4h** and its possible regioisomer, 1-azido-1-phenyl-2-butene (**4h′**), calculated by Gaussian 03W at the B3LYP/6-31(d) level. According to the calculation, **4h** is more stable by 5.1 kcal mol^{-1} than **4h′**, rationalizing the preferred formation of **4h** to **4h′**. The same site-selective substitution of **1h** with a cyanide ion was also observed.[6] Although simple benzyl alcohol **1j** did not react at all, activated primary benzylic alcohol **1k** underwent the azidation in 26% yield with TMSCl, but in 13% yield with AcCl, proving that using TMSCl is preferable to using AcCl as a source of HCl for the azidation reaction. An addition of a small amount of water to the reaction made no improvements of the poor yield, only showing the same yield of 26%.

Attempts to apply the method for the azidation of a secondary aliphatic alcohol **1l** and a tertiary aliphatic alcohol **1m** were not successful. On the other hand, tertiary benzylic alcohol **1n** gave the corresponding azide in almost quantitative yield.

When the trimethylsilyl ether of benzhydrol **5b** was subjected to the azidation conditions, the corresponding azide product was obtained in almost quantitative yield (Fig. 2).



5a 49%[a] ; 9%[a,b] **5b** 98%[a]

Fig. 2 Azidation of dibenzhydril ether (**5a**) and benzhydril trimethylsilyl ether (**5b**). (a) The ^{1}H-NMR yield based on mesitylene as the internal standard. Reaction conditions: 0.5 mmol of **5a** or 1 mmol of **5b**, 2 mmol of Me_3SiN_3, 0.06 mmol of TMSCl, 50 mg of Na-Mont and 5 mL of CH_2Cl_2. (b) Na-Mont was activated at 135 °C in vacuum for 1 h prior to the reaction, CH_2Cl_2 was distilled from CaH_2 and used immediately after the distillation.

During the optimization of the reaction conditions, we observed that when a mixture of **1a**, Na-Mont, TMSCl, and $TMSN_3$ was stirred for 10 min at RT, **4a** was afforded in 93% yield together with the symmetrical ether of benzhydrol **5a** in 2% yield (Table 1, entry 16). When the stirring period was prolonged, the yield of **4a** increased along with the disappearance of **5a**, indicating that **5a** seemed to be one of the intermediates in the azidation.

To further elucidate the mechanism of the azidation, **5a** was subjected to the standard azidation conditions. After a 40 min reaction, **4a** was formed in 49% yield together with 49% of the intact **5a**. In contrast, when the reaction was performed using activated Na-Mont and anhydrous CH_2Cl_2, the yield of **4a** dropped to 9%, suggesting the important role of trace water in the azidation (Fig. 2). Based on these results together with the other observations on the azidation, we proposed a plausible mechanism for this azidation method as shown in Fig. 3.

The reaction is most likely initiated by the hydrolysis of TMSCl by water included in the Na-Mont or the solvent to generate an equimolar amount of HCl, which is then trapped by the Na-Mont. The HCl inside the Na-Mont promotes the generation of a carbenium ion from an alcohol through protonation and subsequent dehydration. The involvement of carbenium ion-like species during the azidation reaction was confirmed by the azidation of (*R*)-1-phenylethanol (98% ee) which yielded a racemic mixture of the corresponding azides in 37% yield.[16] The carbenium ion then reacts with $TMSN_3$ to generate the corresponding azide product as well as trimethylsilanol which is produced by the reaction with water. The regeneration of a proton in the last step of the reaction explains why the subsequent azidation can be repeated without any need to supply more TMSCl.[17]

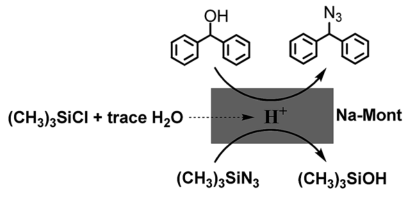


Fig. 3 Plausible mechanism.

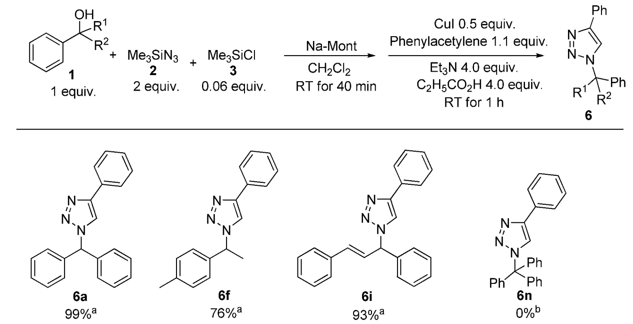


Fig. 4 One-pot synthesis of 1,2,3-triazoles from alcohols. (a) The isolated yield from column chromatography with using hexane/ethyl acetate as eluents.(b) The reaction mixture was stirred for 4.5 h.

One of the most important applications of azides in organic synthesis is the Cu(I)-catalysed Huisgen cycloadditions of azides to alkynes to produce 1,2,3-triazoles.[18] We also investigated the possibility to perform a one-pot synthesis of 1,2,3-triazoles from benzylic alcohols *via* the azidation and the successive click reaction.[19]

After a screening of the reaction conditions, we found that the combination of CuI catalyst with Et_3N and propanoic acid was suitable to perform the one-pot synthesis of 1,2,3-triazole derivatives. A 0.5 equiv. of CuI was employed in the one-pot synthesis since cycloaddition involving bulky azides, such as **4a**, tends to take a longer time to reach completion.[20] Benzylic azides **4a**, **4f**, and **4i** underwent the one-pot cycloaddition to give the corresponding triazole derivatives in 99%, 76%, and 93% yields, respectively (Fig. 4). However, the attempt to synthesize the 1,2,3-triazole from a tertiary benzylic azide **4n** failed, which is probably due to steric effects of such a bulky azide.[21]

In conclusion, we developed a new and practical method to convert natural montmorillonite into a solid acid catalyst using a catalytic amount of TMSCl. The acidic montmorillonite effectively catalysed the azidation of various benzylic alcohols at ambient temperature. The reaction system allows the one-pot synthesis of 1,2,3-triazole derivatives in combination with the CuI catalysis.

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