An Efficient Synthesis of Dihydrobenzo[*c*]azepines from Morita–Baylis–Hillman Adducts via Pictet–Spengler Reaction

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Various dihydrobenzo[*c*]azepines were synthesized in good yields via Pictet–Spengler cyclization protocol from tosylamide derivatives of Morita–Baylis–Hillman adducts and 1,3,5-trioxane. The synthesis was carried out in the presence of easily removable montmorillonite K-10 in short time in high yields.

Keywords: Dihydrobenzo[*c*]azepines, Pictet–Spengler reaction, Morita–Baylis–Hillman adduct, 1,3,5-Trioxane

Introduction

Benzo[*c*]azepines, dihydrobenzo[*c*]azepines, and various polycyclic benzo[*c*]azepine derivatives have been found in many biologically important substances.[1,2] Dihydrobenzo [*c*]azepines could be synthesized by many approaches including palladium-catalyzed Heck reaction of *N*-allylamines,[1a,b] ring-closing metathesis (RCM) reaction of *N*-allylamines,[1c] synthesis of benzazepinium derivative using Fischer-type alkoxycarbene, and a following reduction process.[1d] Our group also reported the synthesis of polycyclic benzo[*c*]azepine derivatives by palladium-catalyzed cyclization.[2d–f]

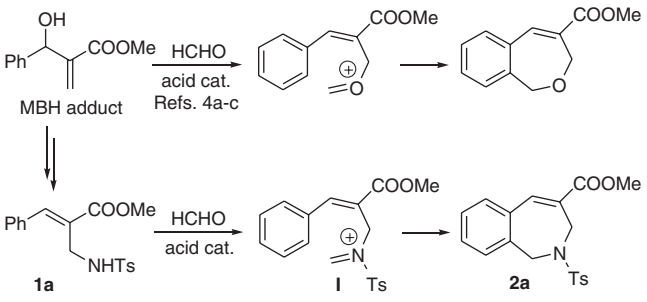
Recently, Morita–Baylis–Hillman (MBH) adducts have been used for the syntheses of various cyclic compounds.[3] Basavaiah *et al*. reported the synthesis of 2-benzoxepines from MBH adducts and formaldehyde in the presence of sulfuric acid.[4a] Later, Das *et al*. also reported the synthesis of same compounds using silica-supported perchloric acid.[4b] Very recently, Bakthadoss *et al*. also reported the synthesis 2-benzoxepines from MBH adducts and cycloaddition reaction of 2-benzoxepines with azomethine ylide.[4c] Although some polycyclic dihydrobenzo[*c*]azepine derivatives have been synthesized from MBH adducts via Pictet–Spengler reaction of *N*-acyliminium ion,[2g,k] there was no report on the synthesis of basic dihydrobenzo[*c*]azepine skeleton, a nitrogen analog of 2-benzoxepine (*vide infra*, Scheme 1), from MBH adducts.

Results and Discussion

In these respects, we reasoned out that dihydrobenzo[*c*]azepine could be synthesized via a Pictet–Spengler reaction of *N*-sulfonyliminium ion intermediate **I**,[5,6] as shown in Scheme 1. Such a Pictet–Spengler type reaction has been carried out in the presence of montmorillonite K-10[7,8] or heteropolyacids (HPAs).[9] As noted above, sulfuric acid and silica-supported perchloric acid have also been used in *oxa*-Pictet–Spengler reaction.[4]

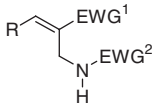
The starting material **1a** was prepared from MBH adduct by a sequential bromination and substitution reaction with tosylamide according to the reported method.[10] Based on our recent successful achievement using montmorillonite K-10,[7a] we examined the reaction of **1a** and 1,3,5-trioxane in refluxing 1,2-dichloroethane in the presence of montmorillonite K-10 (100%, w/w). To our delight, **2a** was formed in high yield (93%) in short time (2 h). The reaction was ineffective at room temperature.[11] Although the benzene ring of **1a** is conjugated with an electron-withdrawing ester group, the Pictet–Spengler reaction with formaldehyde proceeds effectively. Similar Pictet–Spengler reaction involving an electron-deficient arene moiety has been reported in some cases in the presence of a strong acid catalyst such as methanesulfonic acid[2g] or triflic acid.[2i,k]

Encouraged by the successful results, various substrates **1b–l** were prepared according to the reported method,[10] and the synthesis of corresponding dihydrobenzo[*c*]azepines was examined as summarized in Table 1. The reaction of **1b** afforded **2b** in good yield (95%). The reaction of **1c** was sluggish under the typical reaction conditions presumably due to the presence of an electron-withdrawing chlorine substituent, and **2c** was isolated in low yield (39%) for a long time (15 h) along with recovered **1c**



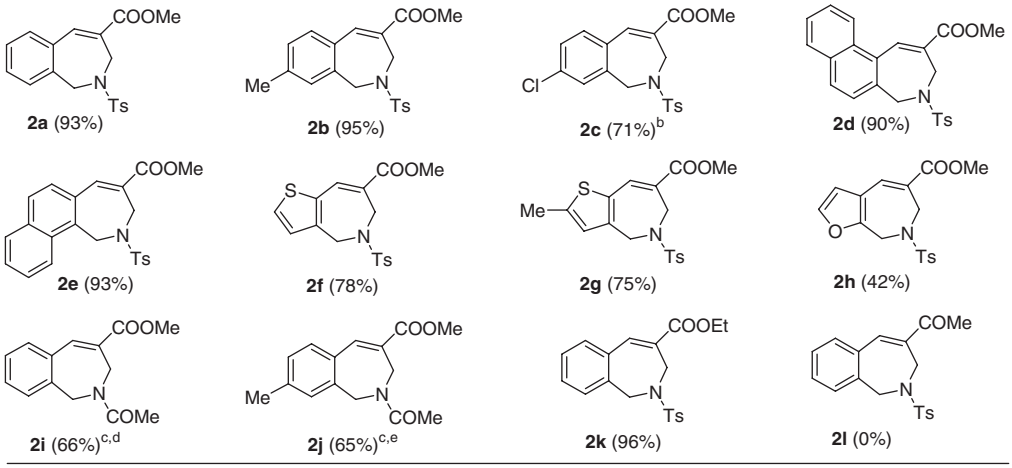
Scheme 1. Synthetic rationale of dihydrobenzo[*c*]azepine **2a**.

Table 1. Synthesis of **2a-l** from **1a-l**.[a]



1a-l

1a: R = Ph, EWG^1 = COOMe, EWG^2 = Ts; **1b**: R = 4-MeC_6H_4, EWG^1 = COOMe, EWG^2 = Ts;
1c: R = 4-ClC_6H_4, EWG^1 = COOMe, EWG^2 = Ts; **1d**: R = 1-naphthyl, EWG^1 = COOMe, EWG^2 = Ts;
1e: R = 2-naphthyl, EWG^1 = COOMe, EWG^2 = Ts; **1f**: R = 2-thienyl, EWG^1 = COOMe, EWG^2 = Ts;
1g: R = 5-Me-2-thienyl, EWG^1 = COOMe, EWG^2 = Ts; **1h**: R = 3-furyl, EWG^1 = COOMe, EWG^2 = Ts;
1i: R = Ph, EWG^1 = COOMe, EWG^2 = COMe; **1j**: R = 4-MeC_6H_4, EWG^1 = COOMe, EWG^2 = COMe;
1k: R = Ph, EWG^1 = COOEt, EWG^2 = Ts; **1l**: R = Ph, EWG^1 = COMe, EWG^2 = Ts.



2a (93%) **2b** (95%) **2c** (71%)[b] **2d** (90%)
2e (93%) **2f** (78%) **2g** (75%) **2h** (42%)
2i (66%)[c,d] **2j** (65%)[c,e] **2k** (96%) **2l** (0%)

[a] Conditions: MBH adduct **1** (0.5 mmol), 1, 3, 5-trioxane (0.5 mmol), K-10 (100%, w/w), $ClCH_2CH_2Cl$, reflux, 2 h.
[b] Carried out with K-10 (100%, w/w) in ODCB (130 °C) for 2 h.
[c] Carried out with K-10 (300%, w/w) in ODCB (150 °C) for 2 h.
[d] *N*-Acetyl rotameric mixture (1:1 based on ^{1}H NMR spectrum in $CDCl_3$; 2:1 in DMSO-d_6).
[e] *N*-Acetyl rotameric mixture (1:2:1 based on ^{1}H NMR spectrum in $CDCl_3$).

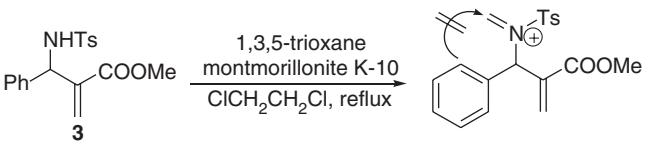
(52%). The reaction at elevated temperature (130 °C) in 1,2-dichlorobenzene (ODCB) gave **2c** in increased yield (71%) in short time (2 h). 1-Naphthyl derivative **1d** gave **2d** in good yield (90%). The reaction of 2-naphthyl derivative **1e** produced **2e** in good yield (93%) as a sole product. The regioselective ring-formation at 1-position of the naphthalene ring is due to a small loss of resonance energy of the naphthalene[12] during the Pictet–Spengler reaction. Dihydrothieno[3,2-*c*]azepine derivatives **2f** and **2g** were prepared in good yields (78 and 75%, respectively).[13] In addition, dihydrofuro[2,3-*c*]azepine derivative **2h** could also be synthesized, albeit in moderate yield (42%).[14]

N-Acetyl derivative **1i** also afforded **2i** in moderate yield (66%) at elevated temperature (150 °C) in ODCB in the presence of an excess amount of K-10 (300%, w/w). The ^{1}H NMR spectrum showed that **2i** exists as a mixture of *N*-acetyl rotamer.[15] The ratio of two rotamers was around 1:1 in $CDCl_3$, whereas 2:1 in DMSO-d_6. When we take ^{1}H NMR in DMSO-d_6 at high temperature (110 °C), the peaks of two rotamers coalesced (see Supporting Information). Similarly, the reaction of **1j** gave **2j** in a similar yield (65%). The ethyl ester **2k** was also synthesized in high yield (96%). The acetyl derivative **1l** failed completely to produce **2l** under the same reaction conditions. The formation of many intractable side products was observed, presumably due to facile aldol and bis-aldol reactions between the acetyl moiety and formaldehyde.[16]

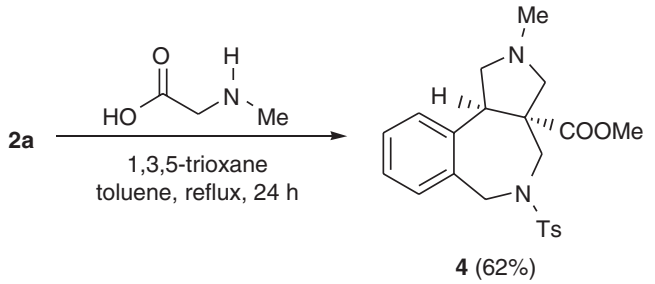
The reaction of *aza*-MBH adduct **3** was also examined under the same reaction conditions, as shown in Scheme 2. No reaction was observed presumably due to unfavorable 5-*endo-trig* cyclization mode, as observed in our previous Pictet–Spengler cyclization of *N*-cinnamyl hydroxylactams.[2g]

In addition, no reaction was observed between **1a** and benzaldehyde (3.0 equiv) under the typical reaction conditions ($ClCH_2CH_2Cl$, K-10, reflux, 2 h). When we carried out the reaction at elevated temperature (150 °C, 3 h) in ODCB, benzaldehyde *N*-tosylimine (PhCH = NTs) was formed in good yield (87%) instead of dihydrobenzo[*c*]azepine derivative. Benzaldehyde *N*-tosylimine must be formed by acid-catalyzed formation of tosylamide from **1a**[17] and the following condensation with benzaldehyde.

As a last experiment, the synthesis of octahydrobenzo[*c*]pyrrolo[3,4-*e*]azepine, **4**,[18] was examined by [3 + 2] cycloaddition reaction of **2a** with azomethine ylide, generated from *N*-methyl glycine and 1,3,5-trioxane.[4c,9c] The reaction



Scheme 2. Unfavorable 5-*endo-trig* cyclization of **3**.



Scheme 3. [3+2] Cycloaddition of **2a** with azomethine ylide.

was carried out in refluxing toluene for 24 h to produce **4** in good yield (62%), as shown in Scheme 3.

Conclusion

In summary, various dihydrobenzo[*c*]azepines were synthesized in good yields via Pictet–Spengler cyclization protocol from tosylamide derivatives of MBH adducts and 1,3,5-trioxane. The synthesis was carried out in the presence of easily removable montmorillonite K-10 in short time in high yields. In addition, octahydrobenzo[*c*]pyrrolo[3,4-*e*] azepine was synthesized by [3 + 2] cycloaddition reaction of dihydrobenzo[*c*]azepine with azomethine ylide, generated from *N*-methyl glycine and 1,3,5-trioxane.

Experimental

Typical Procedure for the Synthesis of 2a**.** A mixture of **1a** (173 mg, 0.5 mmol), 1,3,5-trioxane (45 mg, 1.5 mmol of HCHO), montmorillonite K-10 (173 mg, 100%, w/w) in 1,2-dichloroethane (1.5 mL) was heated to reflux for 2 h. The reaction mixture was filtered through a pad of Celite and washed thoroughly with CH_2Cl_2. After removal of solvent and column chromatographic purification process (hexanes/EtOAc, 5:1), compound **2a** was obtained as a white solid, 166 mg (93%). Other compounds were prepared similarly, and the selected spectroscopic data of **2a**, **2f**, **2h**, **2i**, and **4** are as follows.

Compound **2a**: 93%; white solid, mp 172–174 °C; IR (KBr) 1705, 1339, 1261, 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.32 (s, 3H), 3.81 (s, 3H), 4.48 (s, 2H), 4.52 (s, 2H), 7.03 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 6.9 Hz, 1H), 7.18–7.32 (m, 3H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.39, 50.45, 52.31, 52.75, 126.98, 127.94, 128.52, 128.74, 129.11, 129.74, 132.83, 133.42, 136.32, 137.61, 139.75, 142.87, 166.82; ESIMS *m/z* 358 [M^++H]. Anal. Calcd for $C_{19}H_{19}NO_4S$: C, 63.85; H, 5.36; N, 3.92. Found: C, 63.97; H, 5.61; N, 3.78.

Compound **2f**: 78%; white solid, mp 142–144 °C; IR (KBr) 1702, 1343, 1270, 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.34 (s, 3H), 3.79 (s, 3H), 4.57 (s, 2H), 4.75 (s, 2H), 6.91 (d, *J* = 5.1 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 2H), 7.26 (s, 1H), 7.35 (d, *J* = 5.1 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.45, 49.29, 50.01, 52.24, 125.62, 126.99, 128.97, 129.03, 129.36, 130.97, 133.45, 136.57, 140.98, 143.13, 166.53; ESIMS *m/z* 386 [M^++Na]. Anal. Calcd for $C_{17}H_{17}NO_4S_2$: C, 56.18; H, 4.71; N, 3.85. Found: C, 56.41; H, 4.69; N, 3.93.

Compound **2h**: 42%; white solid, mp 124–126 °C; IR (KBr) 1704, 1345, 1278, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.36 (s, 3H), 3.79 (s, 3H), 4.40 (s, 2H), 4.79 (s, 2H), 6.20 (d, *J* = 1.8 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.20 (s, 1H), 7.28 (d, *J* = 1.8 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.45, 46.98, 48.66, 52.12, 112.32, 117.57, 126.75, 127.13, 129.23, 131.99, 136.22, 141.92, 143.49, 152.66, 166.37; ESIMS *m/z* 348 [M^++H]. Anal. Calcd for $C_{17}H_{17}NO_5S$: C, 58.78; H, 4.93; N, 4.03. Found: C, 58.72; H, 5.17; N, 3.89.

Compound **2i**: 66% (two rotamers, 1:1); white solid, mp 132–134 °C; IR (KBr) 1708, 1653, 1277, 1258 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 24 °C) δ 2.05 (s, 3H), 2.10 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 4.52 (s, 2H), 4.54 (s, 2H), 4.56 (s, 2H), 4.80 (s, 2H), 7.16–7.22 (m, 1H), 7.24–7.45 (m, 7H), 7.70 (s, 1H), 7.78 (s, 1H); ^1H NMR (DMSO-d_6, 500 MHz, 110 °C) δ 1.97 (s, 3H), 3.81 (s, 3H), 4.63 (br s, 2H + 2H), 7.35 (br s, 3H), 7.47 (br s, 1H), 7.62 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.58, 21.61, 48.09, 50.48, 51.16, 52.23, 52.33, 53.27, 127.64, 127.71, 128.28, 128.60, 129.34, 129.42, 129.92, 130.42, 132.36, 133.02, 133.40, 134.39, 138.06, 138.51, 139.04, 140.59, 166.95, 167.06, 169.34, 170.34; ESIMS *m/z* 246 [M^++H]. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.80; H, 6.33; N, 5.69.

Compound **4**: 62%; white solid, mp 170–172 °C; IR (KBr) 1734, 1340, 1276, 1261, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.35 (s, 3H), 2.39 (s, 3H), 2.45 (d, *J* = 10.2 Hz, 1H), 2.80 (d, *J* = 12.6 Hz, 1H), 2.87 (dd, *J* = 9.3 and 6.9 Hz, 1H), 3.10–3.18 (m, 2H), 3.77 (s, 3H), 3.79 (d, *J* = 12.6 Hz, 1H), 4.35 (d, *J* = 14.7 Hz, 1H), 4.39 (t, *J* = 6.9 Hz, 1H), 4.58 (d, *J* = 14.7 Hz, 1H), 6.80 (d, *J* = 7.2 Hz, 1H), 7.05 (t, *J* = 7.2 Hz, 1H), 7.16–7.28 (m, 4H), 7.63 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.45, 41.99, 45.59, 48.16, 48.99, 52.90, 56.33, 60.23, 63.95, 127.01, 127.11, 127.13, 128.66, 129.56, 129.78, 130.94, 136.51, 139.09, 143.33, 175.05; ESIMS *m/z* 415 [M^++H]. Anal. Calcd for $C_{22}H_{26}N_2O_4S$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.56; H, 6.49; N, 6.47.

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Supporting Information. Additional supporting information is available in the online version of this article.

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