Synthesis of Functionalized Methyl-Substituted Bicyclo[1.1.1]pentanes

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Synthesis of new functionalized methyl-substituted bicyclo[1.1.1]pentanes for medicinal chemistry is presented. All the products were obtained in multigram quantities with decent yields. The synthetic approaches reported are facile and scalable. We hope that this work will help process chemists at pharmaceutical companies with the preparation of bioactive bicyclo[1.1.1]pentanes suggested by medicinal chemists for clinical trials.

Introduction

The benzene ring is one of the most prevalent structural motifs in drugs and natural products. In particular, 727 FDA-approved drugs contain a benzene ring [1]. In 2012, Stepan et al. showed that bicyclo[1.1.1]pentane (BCP) mimics the *para*-substituted benzene ring in biologically active compounds [2]. Currently, BCPs are actively used in synthetic and medicinal chemistry [3–12]. More than 300 patents on the use of BCPs in drug discovery projects appeared since 2012. However, due to low synthetic availability, aliphatic substitutions in these compounds remain relatively rare.

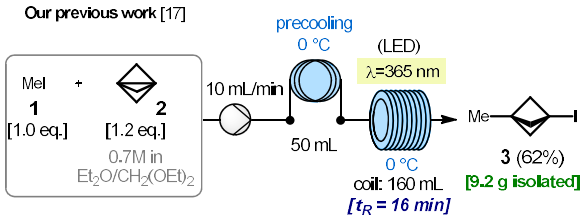


Figure 1. Our previous work on bicyclo[1.1.1]pentanes.

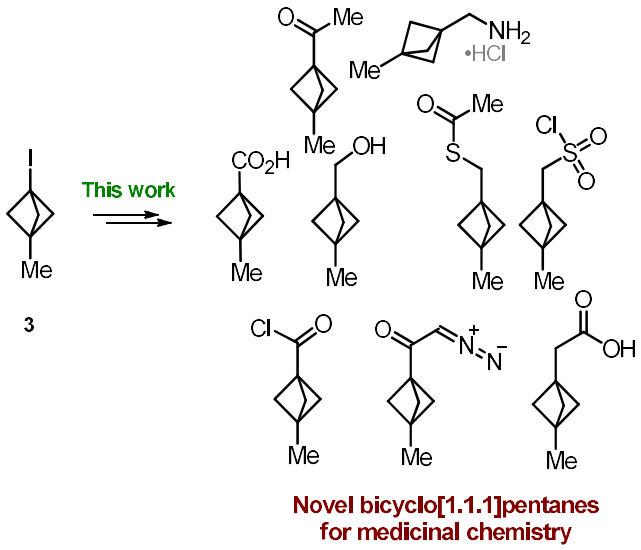


Figure 2. 1-methyl-bicyclo[1.1.1]pentane derivatives.

In particular, the literature contains isolated examples of the reaction of iodomethane with propelanes for the synthesis of methyl-substituted BCPs [13–16]. Hence, despite their potential, the scalable synthesis of methyl-substituted BCPs remains underexplored, representing a valuable area for

further development. Recently, we developed an efficient photochemical protocol for the synthesis of alkyl-substituted bicyclo-[1.1.1]pentane iodides (Figure 1) [17].

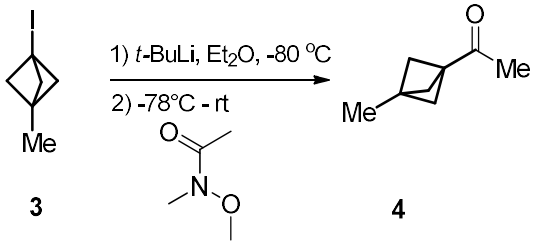
In this work, we report on the unknown modifications of methyl-bicyclo[1.1.1]pentane iodide **3** towards the novel medicinal chemistry-related building blocks (**Figure 2**).

Experimental part

Methods

NMR spectra were recorded at 400 and 500 MHz ^{1}H frequencies. Mass spectra were recorded on an LCMS instrument with chemical ionization (CI) or a GCMS instrument with electron impact ionization (EI).

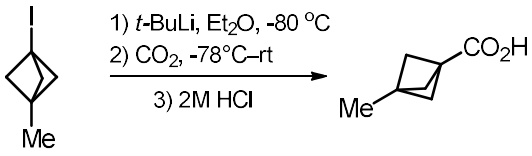
*1-(3-Methylbicyclo[1.1.1]pentan-1-yl)ethanone **(4)***



3 **4**

To a solution of **3** (23 g, 0.11 mol, 1.00 equiv) in dry Et_2O (~300 mL) was added a 1.9M t-BuLi solution in pentane (110 mL, 0.22 mol, 2.10 equiv) dropwise at -80 – -85 °C under Ar atmosphere. After that, the reaction mixture was stirred at this temperature for 10 min, than N-methoxy-N-methylacetamide (3.7 g, 0.016 mol, 1.10 equiv) in Et_2O (10 ml) was added dropwise over 5 min. The reaction mixture was stirred overnight at room temperature, and then washed with water (2 × 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by vacuum distillation to give the desired product 1-(3-methylbicyclo[1.1.1]-pentan-1-yl)ethenone **4**. Yield 9.5 g, 0,077 mol, 70%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.07 (d, J = 1.9 Hz, 4H), 1.87 (s, 6H), 1.17 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d6) δ 206.35, 52.37, 43.98, 35.51, 25.64, 17.56.

*3-Methylbicyclo[1.1.1]pentane-1-carboxylic acid **(5)***

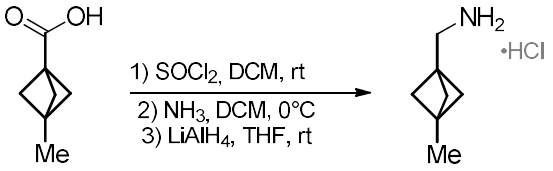


3 **5**

To a solution of **3** (395 g, 1.89 mol, 1.00 equiv) in dry Et_2O (~5 L) was added a 1.9M t-BuLi solution in pentane (2 L, 3.79 mol, 2.10 equiv) dropwise at -80 – -85 °C under Ar atmosphere. After that, the reaction mixture was stirred at this temperature for 10 min and poured on freshly crushed dry ice (~1.7 kg, 38 mol, 20.00 equiv). The reaction mixture was warmed to room temperature and diluted with distilled water (10 L). The layers were separated. The aqueous layer was washed with MeOtBu (4 × 500 mL), acidified with 2M HCl to pH ~ 2, and extracted with MeOtBu (5 × 1 L). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The final product was purified by distilling of pivalic acid under reduced pressure (100 °C, 1 mm Hg). Slight sublimation

of target acid was observed. The final product washed with hexane (~ 400 mL), and dried. Yield: 183 g, 1.45 mol, 77%, white solid, m.p. = 122-123 °C. ^{1}H NMR (400 MHz, DMSO-d6): δ 12.16 (br s, ^{1}H), 1.82 (s, 6H), 1.14 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d6): δ 171.0, 52.5, 37.5, 35.8, 17.7 ppm. HRMS (ESI-TOF) m/z: [M - H]- calcd for $C_7H_9O_2$, 125.0603; found 125.0602.

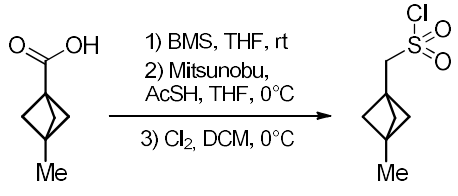
(3-Methylbicyclo[1.1.1]pentan-1-yl)methanamine hydrochloride ***(8)***



5 **8**

To a stirred solution of **5** (25 g, 0.19 mol) in dry DCM (300 ml), was added drop of DMF followed dropwise addition of thionyl chloride (42 ml, 0.59 mol, 3 eqv.). The reaction mixture was stirred at r.t. until gas release was complete. The mixture was concentrated and methylbicyclo[l.l.l]pentane-l-carbonyl chloride (27 g, 0.18 mol, 99% yield) **6** ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05 (d, J = 1.6 Hz, 6H), 1.27 – 1.16 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.86, 54.31, 45.41, 36.47, 17.35.w. Which was used in the next step without further purification. A 1 L round-bottomed flask was charged with methylbicyclo[l.l.l]pentane-l-carbonyl chloride (27 g, 0.18 mol) in DCM (500 mL). Ammonia was bubbled through the solution for 30 minutes. After stirring for 2 hours the reaction was filtered and evaporated to give 3-methylbicyclo[1.1.1]pentane-1-carboxamide **7** (21 g, 0.17 mol, 95% yield). ^{1}H NMR (500 MHz, DMSO-d6) δ 7.09 (d, J = 9.5 Hz, 1H), 6.79 (s, 1H), 1.73 (s, 6H), 1.11 (s, 3H). Which was used in the next step without further purification. To a stirred solution of **7** (21 g, 0.17 mol) in THF (500 mL) was added $LiAlH_4$ (7.7 g, 0.2 mol, 1.2 eqv) at 0°C under an Ar atmosphere. The resulting mixture was stirred for 16 h at room temperature. To the mixture was added aqueous NaOH to pH 9 with saturated. The resulting mixture was extracted with MTBE (5 x ~50 ml). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and were subsequently filtered. The filtrate was cooled to 0°C and HC1 (4M in dioxane, 100 mL) was added dropwise. The reaction was stirred at rt for 30 min and then concentrated in vacuo to provide a white solid. The white solid was triturated with Et_2O to provide (3-methylbicyclo[1.1.1]pentan-1-yl)methanamine hydrochloride **8**. Yield over three steps: 12 g, 0.1 mol, 50%, white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.03 (s, 3H), 2.83 (s, 2H), 1.61 (s, 6H), 1.13 (s, 3H).

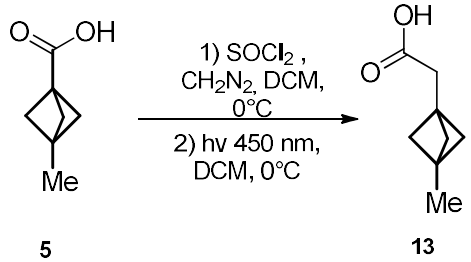
(3-Methylbicyclo[1.1.1]pentan-1-yl)methanesulfonyl chloride ***(11)***



5 **11**

To a solution of **5** (50 g, 0.38 mol) in THF (600 mL) at rt was added $BH_3 \cdot Me_2S$ (43 ml, 0.45 mol, 1.2 eqv.) dropwise. The mixture was stirred at rt 15h, cooled to 0 °C, quenched with MeOH, and concentrated under reduced pressure. Crude products were dissolved in MTBE (500 mL) and was washed with saturated aqueous $NaHCO_3$ (4 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford (3-methylbicyclo[1.1.1]pentan-1-yl)methanol **9**. Yield: 38 g, 0.34 mol, 90%, colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 3.54 (s, 2H), 1.56 (s, 6H), 1.39 (s, 1H), 1.16 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 63.46 – 63.29 (m), 50.38, 39.67, 36.66, 18.48. Which was used in the next step without further purification. Triphenylphosphine (133 g, 0.51 mol, 1.5 eqv) was added to THF (1.2 L) in an 2 L reactor under Ar atmosphere. The resulting solution was cooled down to 0°C. DEAD (100 ml, 0.51 mol, 1.5 equiv) was added into the solution dropwise and the resulting mixture was stirred for 15 min at 0°C. thioacetic acid (55 mL, 0,68 mol, 2.00 equiv) and **9** (38 g, 0.34 mol, 1 equiv) were dissolved in tetrahydrofuran (200 mL) under Ar. This solution was added dropwise into the reaction vessel at 0°C. The resulting mixture was stirred at rt for 15 h and concentrated to dryness. The product mixture was washed with Hexane/MTBE 7/3 (2 L). The filtrate was concentrated to dryness. The residue obtained was purified by distillation under reside pressure (1 mmHg), to afford S-((3-methylbicyclo[1.1.1]pentan-1-yl)methyl) ethanethioate **10** (38 g, 0.22 mol, yield 66%) as a light yellow. ^1H NMR (500 MHz, $CDCl_3$) δ 2.98 (s, 2H), 2.31 (s, 3H), 1.52 (s, 6H), 1.12 (s, 3H). Which was used in next step. The corresponding **10** (38 g, 0.22 mol) was dissolved in CH_2Cl_2 (500 mL), then water (100 mL) was added, and the resulting mixture was cooled to 0°C. After, Cl_2 was bubbled through the stirred reaction mixture until it became yellow green. The layers were separated, the organic phase was washed with water (2×100 mL), aqueous solution of Na_2SO_3 (2×200 mL) and aqueous solution of $NaHCO_3$ (2×200 mL), dried over sodium sulfate and concentrated to dryness to afford (3-methylbicyclo-[1.1.1]pentan-1-yl)methanesulfonyl chloride **11**. Yield over three steps: 41%, 29 g, 0,154 mol, light yellow liquid. ^1H NMR (500 MHz, $CDCl_3$) δ 3.87 (d, J = 1.5 Hz, 2H), 1.88 (d, J = 1.5 Hz, 6H), 1.20 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl3) δ 67.16, 53.61, 38.06, 32.73, 17.72 ppm.

2-(3-Methylbicyclo[1.1.1]pentan-1-yl)acetic acid ***(13)***



5 13

To a stirred solution of **5** (10 g, 0.076 mol) in dry DCM (100 ml), was added drop of DMF followed dropwise addition of thionyl chloride (17 ml, 0.236 mol, 3 eqv.). The reaction mixture was stirred at r.t. until gas release was complete. The mixture was concentrated dryness and methylbicyclo-[l.l.l]pentane-l-carbonyl chloride was used in the next step without further purification. A solution of **6** in Et_2O (200 mL), was cooled to 0 °C in Ar atmosphere, and diazomethane (~0.16 mol, 2.20 equiv) solution in pentane previous prepared by typical procedure was added dropwise over 10 min. The reaction mixture was stirred 5 h at room temperature, and then concentrated in vacuo to afford crude 2-diazo-1-(3-methylbicyclo[1.1.1]pentan-1-yl)ethenone **12** (~10 g, 0.072 mol, 95% yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25 (s, 1H), 1.83 (s, 7H), 1.14 (s, 3H). Which was used in the next step without further purification. The product (10 g, 0.072 mol, 1.00 equiv) was dissolved in Dioxane/H_2O 7/3 (~1000 L) and Na_2CO_3 (38 g, 0.36 mol, 5 eqv). The mixture was stirred 2 h at 15°C under irradiation by KessilLamp 365 nm. After the solution was concentrated in vacuo to 1/5 volume, diluted by water and extracted by MTBE (2 × 200 mL). Water layer was acidified to pH 5 with HCl (aq.). The resulting mixture was extracted with MTBE (3 x 100 ml). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and then concentrated in vacuo to afford 2-(3-methylbicyclo[1.1.1]pentan-1-yl)acetic acid **13**. Yield over three steps 58% 6.2 g, 0,044 mol, , white solid ^{1}H NMR (500 MHz, DMSO-d6) δ 11.94 (s, 1H), 2.32 (s, 2H), 1.56 (s, 6H), 1.10 (s, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d6) δ 172.78, 52.89, 37.69, 36.59, 35.96, 18.53. GCMS (M+H)+: 138.8.

Results and discussion

With a practical and scalable protocol for 1-methyl-3-iodobicyclo[1.1.1]pentane in hand, we utilized this intermediate to synthesize a diverse library of BCP-containing building blocks, featuring one or two functional groups, for applications in medicinal chemistry. Treating methyl-BCP-iodide with t-BuLi in Et_2O, followed by trapping the resulting carbanion with CO_2 and Weinreb–Nahm amide. Also, we found that reaction with dry ice yielded carboxylic acid **5** can be scaled up to ~400 g starting BCP iodide **3** per one butch. Further transformations of the 3-methylbicyclo[1.1.1]pentane-1-carboxylic acid give us a lot of derivatives like primary amine **8** and alcohol **9** from which in turn were obtained ethanethioate **10** and sulfonyl chloride **11**. From carbonyl chloride **6** were obtained diazo ketone **12** and Wolff rearrangement was carried out and obtained acid **13**.

These results underscore the versatility and applicability of methyl-BCP-iodide in advanced synthetic transformations.

Conclusions

Here, we have prepared 10 derivatives of methyl-bicyclo[1.1.1]pentanes for use in medicinal chemistry. Described synthetic approaches afforded multigram-scaled synthesis of the desired compounds with good yields.

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