Multigram Synthesis of 3-Azabicyclo[3.1.1]heptane Derivatives Including Bicyclic Thalidomide Analogs

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Dedicated to the people of Ukraine

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Abstract: An efficient approach to the multigram synthesis of 3-azabicyclo[3.1.1]heptanes is described. The method relied on the intramolecular imide formation in the properly 1,3-functionalized cyclobutane derivative. In turn, the latter compound was obtained via the diastereoselective Strecker reaction of readily accessible 3-oxocyclobutanecarboxylate. The resulting synthetic intermediate – 1-amino-3-azabicyclo[3.1.1]heptane-2,4-dione – was used to synthesize several monoprotected bicyclic diamines valuable as building blocks for medicinal chemistry, as well as a series of bridged analogs of Thalidomide, a known anticancer drug and a component of proteolysis-targeting chimeras (PROTACs).

Introduction

Bicyclic sp^3-enriched systems have gained much attention in design of biologically active compounds as structural analogs of common rings (e.g., benzene, pyridine, piperidine).[1–4] In particular, 3-azabicyclo[3.1.1]heptane (**1**) was proposed to be a bicyclic saturated isostere of pyridine[5] and piperidine[6–12] – two heterocycles most widely used in drug discovery (Figure 1, *A*).[13–15] Some known biologically active 3-azabicyclo[3.1.1]heptane derivatives include potent aromatase inhibitors[16] or purinergic receptor $P2Y_{14}$ antagonists (Figure 1, *B*).[17]

Reported methods for the construction of 3-azabicyclo[3.1.1]-heptane system (Scheme 1) relied on thermal (*A*),[18–20] photochemical (*B*),[16,21–23] or metal-catalyzed[24] intramolecular [2+2] cycloaddition, recyclization of 2-oxaspiro[3.3]heptanes (*C*),[5] double Mannich reaction of cyclobutanone,[6] or cyclization of 1,3-substituted cyclobutane-derived amino esters (*D*).[7,25–27] Herein, we report very efficient approach to the multigram synthesis of 3-azabicyclo[3.1.1]heptanes based on the cyclization of cyclobutane-derived 1,3-dicarboxylic acid derivative **1** (Scheme 1, *E*). Notably, somewhat related approach, i.e., cyclization of truxillic acid amides, was used in the very first synthesis of 3-azabicyclo[3.1.1]heptane system reported over a century ago.[28] The key intermediate obtained in our work – bicyclic imide **2** – was transformed into a series of 1-amino-3-azabicyclo[3.1.1]heptane derivatives, including monoprotected diamine building blocks **3** and **4**, as well as bicyclic analogs of Thalidomide. This classical medication is currently used to treat a variety of cancers; recently, it has attracted much attention in design of proteolysis-targeting chimeras (PROTACs) due to its action as a cereblon E3 ligase ligand.[29]

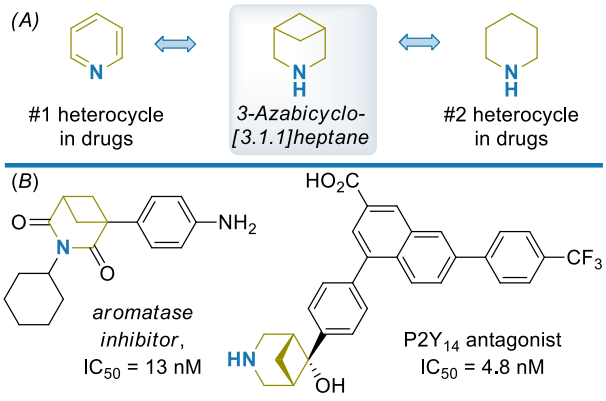
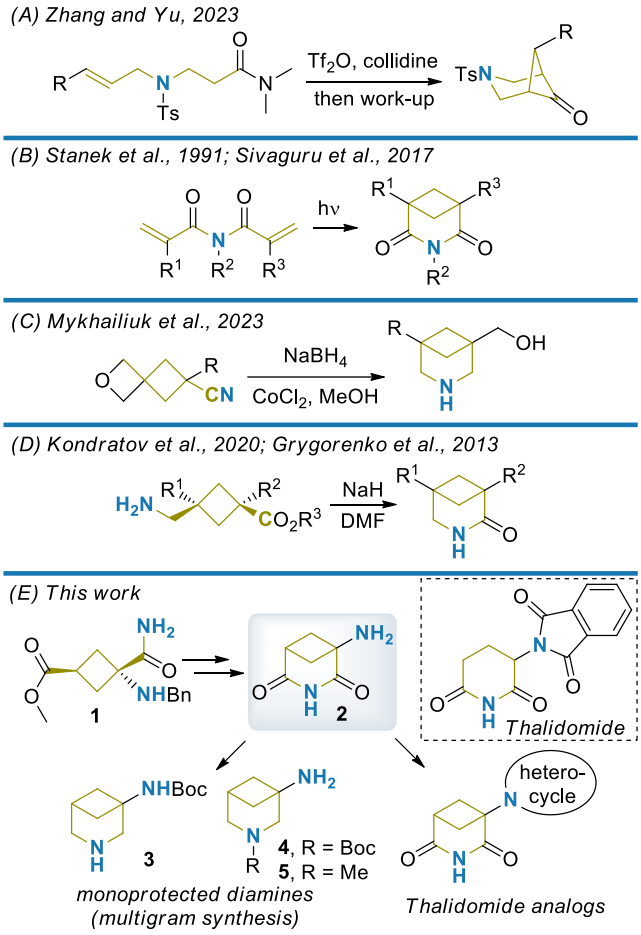


Figure 1. (*A*) 3-Azabicyclo[3.1.1]heptane – isostere of pyridine and piperidine. (*B*) Some biologically active 3-azabicyclo[3.1.1]heptanes.

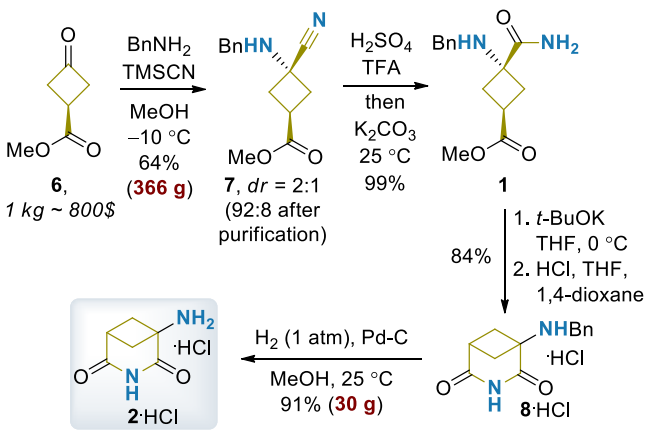


Scheme 1. (*A*–*D*) Known synthetic approaches toward 3-azabicyclo[3.1.1]heptanes. (*E*) The main approach used in this work.

Results and Discussion

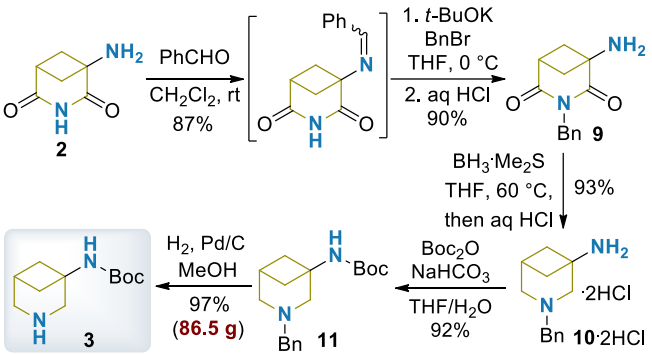
Our synthesis of key intermediate **1** commenced with the modified Strecker reaction of methyl 3-oxocyclobutane-3-carboxylate (**6**) available commercially in kilogram quantities (Scheme 2). Since the Strecker reaction is known to be reversible, the thermodynamically more stable stereoisomer **7** with *trans* position of the two largest substituents, *i. e.*, NHBn and CO_2Me, was formed predominantly (initial *dr* = 2:1). After the chromatographic separation and trituration with *i*-PrOH, almost pure diastereomer **7** was obtained in 64% yield (*dr* = 92:8). Notably, despite the chromatographic purification step, compound **7** could be obtained on up to 366 g scale in a single run.

Partial hydrolysis of the nitrile group in the molecule of **7** was performed upon action of H_2SO_4 in CF_3COOH in nearly quantitative yield; notably, the ester moiety remained intact at these conditions. Amide **1** thus obtained was subjected to cyclization mediated by *t*-BuOK; target derivative **8** bearing the desired bicyclic system was isolated as hydrochloride in 84% yield. Finally, catalytic hydrogenolysis of compound **8**·HCl let to key building block **2**·HCl in 91% yield. The latter step was performed on up to 30-g scale.



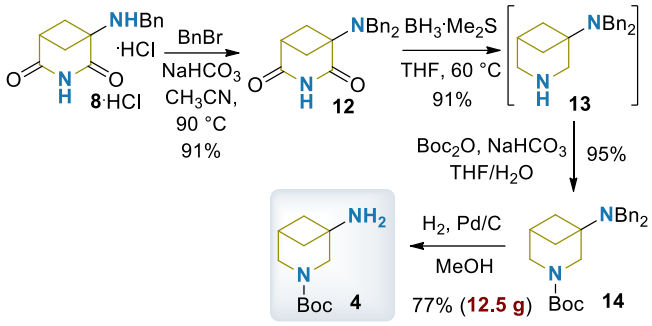
Scheme 2. Synthesis of key building block **2**·HCl.

Synthesis of monoprotected bicyclic diamine **3** started from compound **2**. Since its direct *N*-benzylation at the imide moiety was not selective, protection of the free amino group with benzaldehyde was used (Scheme 3). Further steps after the deprotection included reduction of product **9** (90% yield) with $BH_3{\cdot}Me_2S$ (93% yield), *N*-Boc-protection of amine **10** (92% yield), and catalytic hydrogenolysis of derivative **11** (97% yield, Scheme 3). This six-step reaction sequence provided target building block **3** in 65% overall yield.



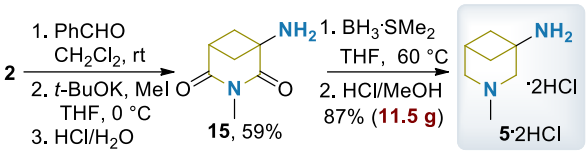
Scheme 3. Synthesis of monoprotected diamine **3**.

Synthesis of building block **4** commenced from the precursor of intermediate **2**·HCl – compound **8**·HCl (Scheme 4). Alkylation of of amine **8** with benzyl bromide provided dibenzyl derivative **12** (91% yield**)**. Reduction of compound **12** with $BH_3{\cdot}Me_2S$ gave intermediate secondary amine **13** (91% yield) that was subjected to *N*-Boc-protection (95% yield). Resulting derivative **14** was transformed into target monoprotected diamine **4** (77% yield) upon exhaustive hydrogenolysis.



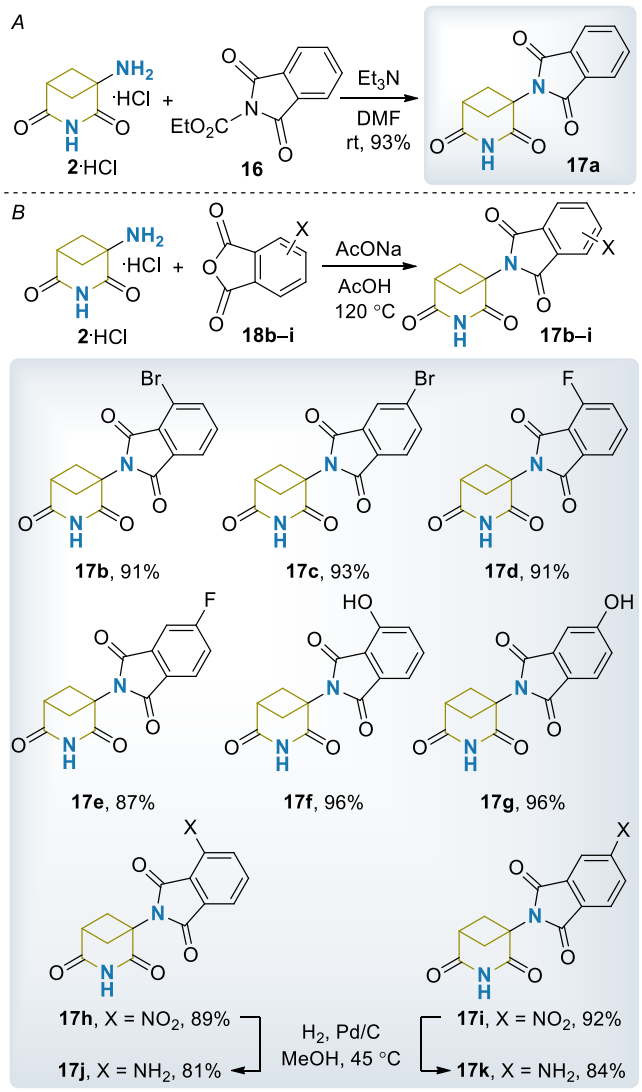
Scheme 4. Synthesis of monoprotected diamine **3**.

Synthesis of amine **5** was performed in analogous manner and started with selective imide methylation in the molecule of **2**, which again required the free amino group protection through imine formation (Scheme 5). *N*-Methylated derivative **15** obtained after the deprotection (68% yield) was subjected to reduction with $BH_3{\cdot}Me_2S$ providing target compound **5** in 87% yield.



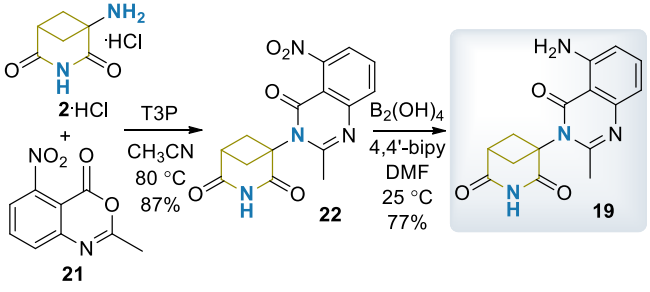
Scheme 5. Synthesis of monoprotected diamine **5**.

In the next part of the study, we focused on the preparation of heterocyclic derivatives of amine **2** – analogues of Thalidomide. In particular, its closest homolog **17a** was prepared in 93% yield by reaction of compound **2** and phthalimide derivative **16** (Scheme 6, *A*). A series of functionalized derivatives **17b–i** were obtained by reaction of **2** and corresponding phthalic anhydrides **18b–i** (87–96% yield); nitro derivatives **17h** and **17i** were transformed into amines **17j** (81%) and **17k** (84%), respectively, upon catalytic hydrogenation (Scheme 6, *B*).



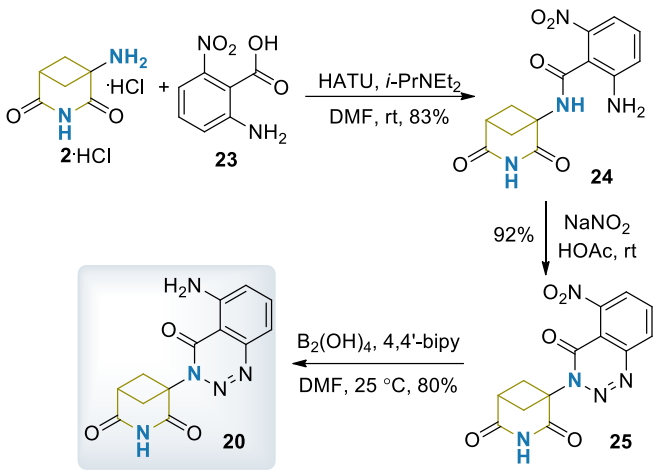
Scheme 6. Synthesis of Thalidomide analogs **17**.

Furthermore, quinazoline- and benzo[*b*][1,2,3]triazine-derived isosteric analogs **19** and **20** were also synthesized. To obtain compound **19**, amine **2** reacted with isatoic anhydride **21** in the presence of propanephosphonic acid anhydride (T3P) to give nitro derivative **22** (87% yield) (Scheme 6). Reduction of compound **22** with $B_2(OH)_4$ in the presence of 4,4′-bipyridine (4,4′-bipy)[30] provided target amine **19** (77% yield). Notably, the catalytic hydrogenation did not work in this case, likely due to the competing heterocycle reduction.



Scheme 6. Synthesis of Thalidomide analog **19**.

For the preparation of compound **20**, amine **2** was subjected to amide coupling with anthranilic acid derivative **23** (Scheme 7). Amide **24** thus formed (83% yield) was diazotized to give benzo-[*b*][1,2,3]triazine **25** (92% yield). Finally, reduction of compound **25** with with $B_2(OH)_4$ – 4,4′-bipy gave target amine **20** (80% yield).



Scheme 7. Synthesis of Thalidomide analog **20**.

Conclusion

An efficient approach to the multigram preparation of 3-aza-bicyclo[3.1.1]alkanes based on the intramolecular imide formation in the properly functionalized cyclobutane derivative is described. Diastereoselective Strecker reaction of readily accessible 3-oxocyclobutanecarboxylate was used to mount the required functional groups onto the cyclobutane ring with proper stereo-chemistry. After selective partial hydrolysis of the nitrile group, the key cyclization into the target bicyclic imide proceeded smoothly upon action of a base (*t*-BuOK). After catalytic debenzylation, 1-amino-3-azabicyclo[3.1.1]heptane-2,4-dione, a key building block and intermediate in this study, was obtained on up to 30 g scale. The utility of the proposed protocols was demonstrated by multigram preparation of monoprotected bicyclic diamines – valuable building blocks for early drug discovery programs. Furthermore, 10 bridged analogs of Thalidomide, a known anticancer drug and an important component of proteolysis-targeting chimeras (PROTACs), was prepared on a gram scale.

Supporting Information

The authors have cited additional references within the Supporting Information.[30, 31]

Acknowledgements

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Conflict of Interest

Most of the authors are / have been employees, trainees, or consulting scientists of Enamine Ltd. that offers all the building blocks described in this paper in the company's catalog.

Experimental section

General

The solvents were purified according to the standard procedures.[31,32] Methyl 3-oxocyclobutane-3-carboxylate **6** and isatoic anhydride **21** were obtained from Enamine stock; all other starting materials were available commercially. Melting points were measured on the MPA100 OptiMelt automated melting point system. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR), on Agilent ProPulse 600 spectrometer (at 500 MHz for ^{1}H and 151 MHz for ^{13}C) and Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. For ^{19}F NMR CCl_3F was used as internal standards. Coupling constants (*J*) are given in Hz. High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer.

Methyl (1*R,3*R**)-3-(benzylamino)-3-cyanocyclobutane-1-carboxylate (7).** To a solution of cyclobutanone **6** (300.0 g, 2.34 mol) in MeOH (2.5 L) neat benzyl amine (263.3 g, 2.46 mol) was added in one portion and the mixture was stirred for 2 h at rt. The resulting solution was cooled to –10 °C in a NaCl/ice bath, and neat TMSCN (464.3 g, 4.68 mol) was added in a dropwise manner at the same temperature. After addition, the bath was removed, and the reaction mixture was left with stirring overnight. The volatiles were removed under reduced pressure and the oily residue was purified by flash column chromatography (hexanes – EtOAc, gradient 1:1 to 1:2 v/v). The major diastereomer **7** was isolated by trituration of the purified mixture with minimum amounts of 2-propanol (*dr* ca. 92:8). Yield 366.0 g, 1.50 mol, 64%.

Methyl (1*R,3*R**)-3-(benzylamino)-3-carbamoylcyclobutane-1-carboxylate (1).** To a pre-cooled to 10 °C solution of **7** (250.0 g, 1.02 mol) in TFA (1250 mL) conc. H_2SO_4 (96%, 250 mL) was added in a dropwise manner with cautious stirring. The reaction mixture was stirred for additional 16 h at 25 °C and then concentrated under reduced pressure. The vessel with viscous residue was cooled in an ice-water bath and the latter was neutralized with ice-cold sat. aq K_2CO_3 to pH 9 (*CAUTION! Slow addition is necessary! Violent reaction occurs!*). The precipitated product was filtered, washed with water (7×1250 mL), and dried under a high vacuum (1 mmHg) to give pure **1**. Yield 262.9 g, 1.00 mol, 98%.

1-(Benzylamino)-3-azabicyclo[3.1.1]heptane-2,4-dione hydrochloride (8·HCl). To a pre-cooled to 0 °C solution of **1** (100.0 g, 0.381 mol) in THF (1.5 L) neat *t*-BuOK (85.6 g, 0.763

mol) was added in several portions keeping the temperature below 5 °C. The reaction mixture was warmed up to rt and stirred for an additional 4 h, then concentrated under reduced pressure. The residual brownish solid was dissolved in water (350 mL), acidified with $NaHSO_4$ (45.7 g, 0.381 mol) and extracted with $CHCl_3$ (4×350 mL). Combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was dissolved in THF (250 mL) and acidified with anhydrous HCl (ca. 3.6 M in dioxane, 110 mL). The precipitate was filtered and dried under a high vacuum (1 mmHg) to give **8**. Yield 85.4 g, 0.320 mol, 84%.

1-Amino-3-azabicyclo[3.1.1]heptane-2,4-dione hydrochloride (2·HCl). Compound **8** (50.0 g, 0.187 mol) was dissolved in MeOH (1 L) and Pd/C (10% w/w, 9.50 g) was added in one portion. The reaction vessel was evacuated and backfilled with H_2 from a balloon (repeated 3 times), and the suspension was kept under H_2 atmosphere with intensive stirring at 45 °C for 24 h. After the reaction was completed (concluded by ^{1}H NMR spectra of the small aliquots of the reaction mixture) the catalyst was filtered off and the filter cake was washed with hot MeOH (5×200 mL). The filtrate was concentrated under reduced pressure to afford pure **2**·HCl. Yield 30.1 g, 0.170 mol, 91%.

Keywords: bicyclic compounds • imides • cyclobutane • thalidomide • building blocks

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