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Technical Note

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A Concise Synthesis of a Tetrahydropyrazolopyrazine Building Block

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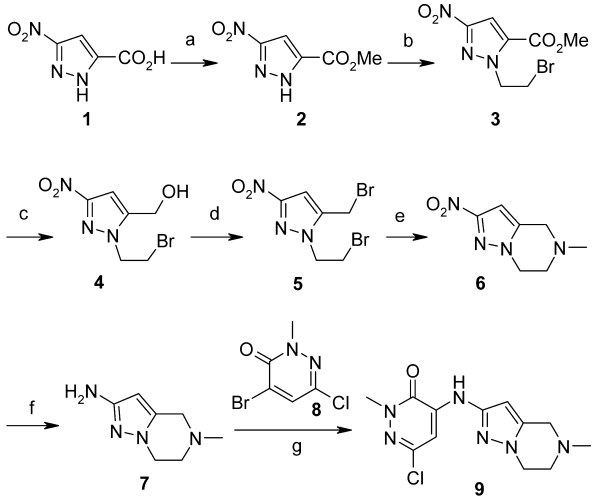
ABSTRACT: A concise synthesis of a tetrahydropyrazolopyrazine building block is described. 5-Methyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazin-2-ylamine was prepared in three steps and 80% yield from 5-nitro-2*H*-pyrazole-3-carboxylic acid. This compound was then coupled with 4-bromo-6-chloro-2-methyl-2*H*-pyridazin-3-one in the presence of sodium *tert*-pentoxide to give the target product in 87% yield. The process was successfully scaled up to a multihundred gram scale.

INTRODUCTION

A recent drug discovery program at Roche required multihundred grams of a heterocyclic building block **9** to prepare the lead compounds for toxicology studies. The original seven-step synthesis described in the patent application,[1] shown in Scheme 1, gave **9** in ∼18% overall yield from **1**. This process is not suitable for the preparation on a multihundred-gram scale for several reasons: (1) three steps required chromatographic purification; (2) bromination using phosphorous bromide in chloroform was low yielding and not environmentally friendly; (3) the alkylation of **2** with 1,2-dibromoethane gave poor regioselectivity; thus, a modest yield was obtained for **3**. An alternative synthesis reported by Barbosa et al.[2] also required chromatographic purification and used undesirable reagents, such as phosphorous bromide. As this building block was required for multiple compounds,[1−3] process research was initiated to develop a scalable and efficient synthesis. Herein, we describe a concise synthesis of **9** that proceeds in four steps and 69% overall yield from commercially available **1**.

Scheme 1. Original synthesis of 9[a]



[a]Reagents and conditions: a) $SOCl_2$, MeOH, overweight; b) 1,2-dibromoethane, K_2CO_3, acetone, chromatography, 49% yield from **1**; c) $LiBH_4$, THF; d) PBr_3, $CHCl_3$, chromatography, 51% yield from **3**; e) CH_3NH_2, THF, 83%; f) H_2, Pd/C, EtOH; g) $Pd_2(dba)_3$, Xantphos, Cs_2CO_3, dioxane, chromatography, 83−93% yield from **6**.

RESULTS AND DISCUSSION

In the original synthesis of **9**, the major issue was the poor regioselectivity in the alkylation step (Scheme 2). The formation of **10** not only lowered the yield of **3**, but also caused difficulties during the purification. We envisioned that an alkylation exclusively at the 2-position can be achieved if the ethylene unit is introduced in an intramolecular manner as shown in Scheme 3. Then, lactam **11** could be reduced by borane to give **6**.

Treatment of **1** with thionyl chloride in the presence of a catalytic amount of DMF gave a dimeric intermediate **13**[4] instead of the acid chloride.[5] A promising result was then obtained from an initial screening study; i.e., when a mixture of **13** and *N*-(2-chloroethyl)methylamine hydrochloride (**14**-HCl) in DMF was treated with triethylamine, the reaction directly gave the cyclization product **11** in 36% isolated yield (Scheme 4). The major issue encountered was that compound **14**-HCl, either purchased from commercial supplier or freshly prepared from 2-methyaminoethanol (**15**), was highly hygroscopic, thus difficult to handle. As the reaction was moisture sensitive, this led to inconsistent yield and purity for the product. Therefore, a process that proceeds without the isolation of **14**-HCl would be desirable and potentially could overcome this issue.

A one pot process that involved four chemical transformations was thus developed and **11** was obtained in 82% yield from **1**. As shown in Scheme 5, a mixture of **1** and **15** was suspended in toluene and thionyl chloride, then a catalytic amount of DMF was added. The reaction mixture was warmed to ∼55 °C to complete the conversion of **15** to **14**-HCl. The formation of the HCl salt prevented it from oligomerization.[6] The conversion of **1** to **13** required higher temperature; thus, the mixture was heated to ∼70 °C and stirred at this temperature for 10 h. After concentration to remove excess thionyl chloride and a portion of the toluene, the remaining suspension was dissolved in DMF; then triethylamine was added dropwise, at <45 °C, to free base **14**-HCl. The coupling and cyclization took place instantaneously to afford **11**; the

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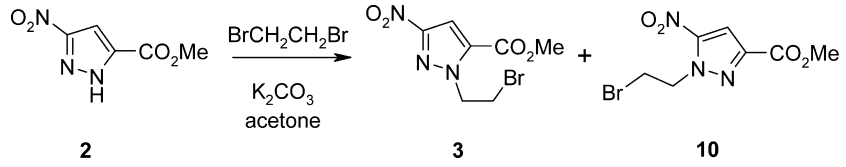
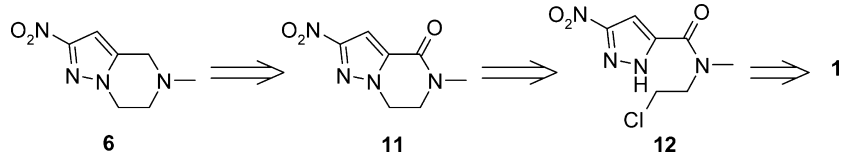
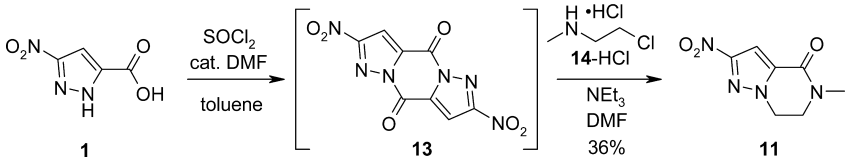
Scheme 2. Non-selective alkylation of 2 with 1,2-dibromoethane



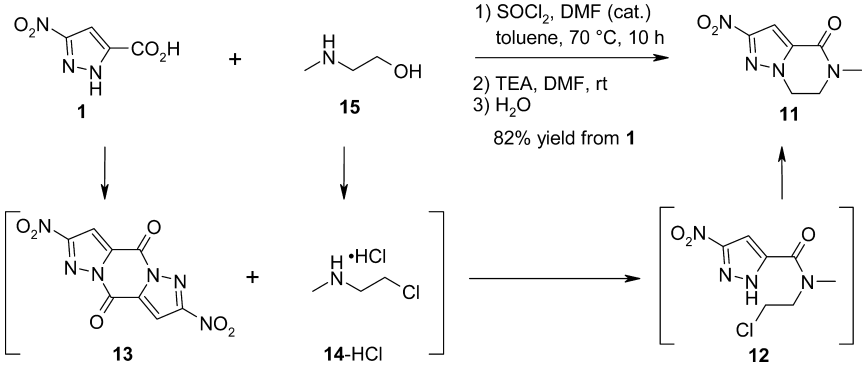
Scheme 3. Retrosynthesis of 6



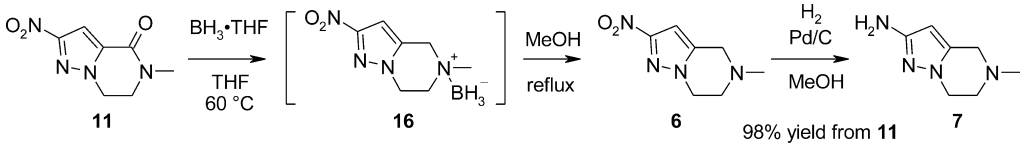
Scheme 4. Preparation of 11 using 14-HCl



Scheme 5. One-pot preparation of 11 from 1 and 15



Scheme 6. Preparation of 7 from 11



presumed intermediate **12** was not detected by LC/MS analysis. After the reaction was complete, the mixture was diluted with water and *n*-heptane. The product precipitated and was isolated by filtration in 82% yield as a tan solid.

The reduction was initially tested by adding solid **11** to a solution of 1 M BH_3·THF (3 equiv) in THF. The reaction was very slow at room temperature but became quite exothermic at reflux. In order to control the exotherm, **11** was suspended in THF and initially heated to 60 °C, then a solution of BH_3·THF was added dropwise over 1 h, and the mixture was stirred at ~60 °C for an additional 2−5 h to give a mixture of **6** and borane complex **16** (Scheme 6). Under these conditions, the amount of borane was reduced to 2 equiv.

To break complex **16**, methanol was added slowly at 55−60 °C and the mixture was stirred at this temperature for 1 h. After solvent exchange to *n*-heptane, product **6** precipitated and was collected by filtration. The crude product thus obtained (containing ~10−15 wt % of boric acid) was directly used in the catalytic hydrogenation step without further purification.

The hydrogenation was carried out in a Parr reactor using 5% Pd/C. A mixture of **6** and the catalyst (0.5 mol %) in methanol under 200 psi hydrogen pressure was heated to 35 °C for 40 h to achieve complete conversion. It was subsequently found that complete hydrogenation could be accomplished in 22 h and at a lower hydrogen pressure (50−100 psi) by heating the mixture to 65 °C.[7] After removing the catalyst, the solvent was exchanged with Me-THF, and then the crystallization was completed by solvent exchange to *n*-heptane. The solid was collected by filtration, washed with *n*-heptane, and dried to give **7** in >99% purity and 98% overall yield from **11**.

In the original process,[1−3] compound **9** was prepared by palladium-catalyzed coupling of **7** with pyridazinone **8**.[8] While

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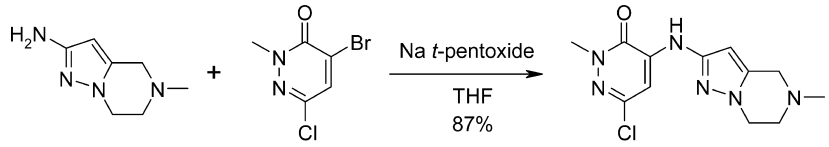
Scheme 7. Coupling of 7 and 8 under transition metal-free conditions



7 8 9

9 was obtained in good yield, the reaction was run under high dilution (up to 70 vol.), and chromatography was required to isolate the product. As a variety of closely related compounds have also been prepared using essentially the same method according to the patent literature,[1−3,8,9] a more robust method preferably without using a transition metal would be highly desirable. Alkylamines have been reported to directly react with analogues of **8**.[10−12] In addition, the coupling of a less reactive arylamine with **8** using potassium *tert*-butoxide as the base has been reported, albeit to give the desired product in low yield of 25%.[8]

Encouraged by this literature precedent, the coupling of **7** and **8** was examined under transition metal-free conditions. The desired product **9** was detected by LC/MS analysis when a mixture of **7** and **8** was treated with a base, such as potassium carbonate, DIPEA, and DBU, in NMP at an elevated temperature. However, none of these conditions gave a reaction that was clean enough for further optimization.

Subsequently, a reasonably clean reaction was achieved when a solution of **7** in THF was treated with 1 equiv of a strong base, such as sodium *tert*-pentoxide, sodium *tert*-butoxide, or potassium *tert*-butoxide, followed by a slow addition of **8**. The reaction using sodium *tert*-pentoxide appeared to be somewhat cleaner than the others. However, in all cases, the reactions always stopped at essentially 50% conversion; HPLC analysis indicated the presence of a mixture of **9** along with unreacted **7** and **8**.

The incomplete reaction suggested that **9** was more acidic than **7**, thus consuming 0.5 equiv of the base. Therefore, addition of one more equiv of base should lead to complete conversion. The addition of the second equiv of sodium *tert*-pentoxide indeed caused the reaction to move forward, but the levels of byproducts also significantly increased. In order to identify the origin of these byproducts, a controlled experiment was conducted by adding **8** to a solution of sodium *tert*-pentoxide in THF. The initially colorless solution became dark purple instantly; HPLC analysis showed that **8** was completely decomposed, and a black tar was formed.

As the controlled experiment clearly indicated that **8** was not stable under strongly basic conditions, the addition order of the reagents was modified as follows to avoid the direct contact of **8** with sodium *tert*-pentoxide. Compound **7** in THF was treated with 1.0 equiv of sodium *tert*-pentoxide in THF at room temperature. Then, 0.5 equiv of **8** in THF was added dropwise at ≤35 °C. After **8** was consumed, HPLC analysis indicated formation of essentially a 1:1 mixture of **7** and **9**. Then, a further 0.5 equiv of sodium *tert*-pentoxide was added, followed by the dropwise addition of 0.25 equiv of **8**. This alternate addition sequence was repeated two more times, each with 0.25 equiv of sodium *tert*-pentoxide and 0.125 equiv of **8**, to give complete reaction according to HPLC analysis. The reaction was then quenched with acetic acid and water. The product **9** was isolated by filtration in 87% yield as a white solid (Scheme 7). The highest dilution now with respect to **9** was 12 vol.

In conclusion, we have developed an efficient synthesis of heterocyclic building block **9**, which was prepared in four steps and 69% overall yield from **1**. The synthesis has been successfully scaled up to make 600 g of the target product in a single batch. The transition metal-free coupling method developed for **9** has been successfully applied to the syntheses of a number of advanced intermediates for various drug discovery programs.

EXPERIMENTAL SECTION

General. HPLC analysis was performed on Agilent Eclipse XDB-C8 (4.6 mm × 50 mm, 1.8 μm) column with 5−100% CH_3CN/H_2O (+0.1% TFA) as mobile phase at flow rate of 1.0 mL/min over 10 min. Compound **8** was prepared in three steps and 77% yield from 3,6-dichloropyridazine using an optimized process based on literature procedures.[8,13]

*5-Methyl-2-nitro-6,7-dihydro-5H-pyrazolo[1,5-a]pyrazin-4-one (**11**).* 2-Methylaminoethanol (220 g, 2.92 mol), toluene (2.68 L) and **1** (383 g, 2.47 mol) were cooled to 15 °C, then thionyl chloride (498 mL, 6.83 mol) was added over 10 min at ≤25 °C, followed by DMF (18.8 mL). The reaction mixture was warmed to 54 °C and stirred for 10 min, then further heated to 70 °C and stirred for 10 h. The resulting suspension was then concentrated at 60 °C/100 mmHg to remove excess thionyl chloride and a portion of the toluene (1.72 L). After cooling to room temperature, the residue was dissolved in DMF (1.9 L), and triethylamine (1.53 L, 11.0 mol) was added at a rate to maintain the internal temperature below 45 °C. The reaction mixture was stirred at room temperature for an additional 90 min; then ∼1.5 L of solvent was removed by concentration at 60 °C/100 mmHg. The residue was cooled to room temperature and diluted with water (4.6 L) and *n*-heptane (500 mL). The suspension was stirred at ambient temperature overnight and at 5 °C for 2 h and then was filtered. The filter cake was washed with water (2 × 1.1 L), and dried to give **11** (390 g, 81.5% yield) as a tan solid. Mp 213 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41(s, 1H), 4.53 (m, 2H), 3.87 (m, 2H), 3.03 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.62, 154.60, 136.58, 102.86, 46.46, 46.19, 33.55; HRMS calcd for $C_7H_9O_3N_4$ [M + H] 197.0669, found 197.0663.

*5-Methyl-2-nitro-4,5,6,7-tetrahydropyrazolo[1,5-a]-pyrazine (**6**).* Compound **11** (554 g, 2.82 mol) and THF (1.11 L) were heated to 60 °C, and a 1 M borane−THF complex (5.82 L, 5.82 mol) was added over 60 min while maintaining the reaction temperature at ∼60 °C. (CAUTION: achieve gentle reflux before adding borane to avoid the possibility of a runaway reaction). The resulting clear solution was stirred at 60 °C for 5 h, quenched with methanol (1.00 L, 24.7 mol) at 55 °C, and stirred at this temperature for 1 h. The resulting solution was then concentrated under reduced pressure to a total volume of ∼4 L. The residue was diluted with *n*-heptane (3.32 L) and reconcentrated to 4 L. Additional *n*-heptane (3.32 L) was added, and the suspension was cooled to room temperature, stirred for 30 min, and filtered. The filter cake was

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washed with *n*-heptane (2.2 L) and then dried to give **6** (579 g, overweight) as a light-yellow solid. Mp 124−125 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.84 (t, J = 0.9 Hz, 1H), 4.21 (m, 2H), 3.63 (s, 2H), 2.91 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.81, 140.49, 98.45, 50.76, 50.64, 47.78, 44.52; HRMS calcd for $C_7H_{11}O_2N_4$ [M + H] 183.0877, found 183.0870.

*5-Methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl-amine (**7**).* A 20 L autoclave reactor was charged with **6** (579 g, 2.82 mol in theory), 5% Pd in charcoal (50% wet, 90 g, 14.4 mmol), and MeOH (5.79 L). The reactor was flushed three times with N_2 and then three times with H_2. After stirring under 200 psi of H_2 for 40 h at 450 rpm, NMR analysis indicated complete reaction. The reaction mixture was filtered through a Celite pad. The filtrate and washes were combined and concentrated at 40 °C under vacuum. The resulting oil was diluted with Me-THF (3.0 L) and then reconcentrated to remove most of solvents. When the product started to crystallize, *n*-heptane (3.0 L) was added. The resulting suspension was cooled to room temperature, stirred for 40 min, and filtered. The filter cake was washed with *n*-heptane (500 mL) and dried to give **7** (420 g, 97.9% yield) as white solid. Mp 85 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.16 (t, J = 0.7 Hz, 1H), 4.55 (br s, 2H), 3.76 (m, 2H), 2.73 (m, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.98, 137.20, 87.88, 51.94, 51.29, 45.74, 44.92; HRMS calcd for $C_7H_{13}N_4$ [M + H] 153.1140, found 153.1131.

*6-Chloro-2-methyl-4-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-ylamino)-2-H-pyridazin-3-one (**9**).* A solution of **7** (45.0 g, 296 mmol) in THF (135 mL) was treated with a solution of sodium *tert*-pentoxide in THF (2.5 M, 120 mL, 300 mmol) and the mixture was stirred at room temperature for 30 min. To the resulting green suspension was added a solution of **8** (33.2 g, 149 mmol) in THF (108 mL) over 15 min at ≤35 °C. The mixture was stirred for an additional 10 min, and a second portion of sodium *tert*-pentoxide in THF (2.5 M, 61.5 mL, 154 mmol) was added. After 10 min, **8** (17.1 g, 76.5 mmol) in THF (54 mL) was added over 10 min, and the mixture was stirred for 5 min. A third portion of sodium *tert*-pentoxide in THF (2.5 M, 31.5 mL, 78.8 mmol) was then added, and after this mixture stirred for 10 min, **8** (9.4 g, 42.0 mmol) in THF (30 mL) was added over 5 min. After an additional 10 min, a final portion of sodium *tert*-pentoxide in THF (2.5 M, 31.5 mL, 78.8 mmol) was added. Then, **8** (9.4 g, 42.0 mmol) in THF (30 mL) was added over 5 min. After stirring for 30 min, LC/MS analysis of the slurry indicated complete reaction. The reaction mixture was quenched with acetic acid (19.0 mL, 332 mmol) in water (161 mL), and ∼270 mL of solvent was removed by concentration at 45 °C/150 mmHg. The residue was diluted with water (270 mL) and reconcentrated to remove an additional 135 mL of solvent. The remaining suspension was stirred at 60 °C for 15 min, cooled to room temperature, and filtered. The filter cake was washed with water (3 × 180 mL) and dried to give **9** (76.0 g, 87.2% yield) as a white solid; 99.47% pure according to HPLC analysis (254 nm). Mp 210−214 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (s, 1H), 7.72 (s, 1H), 6.00 (s, 1H), 4.04 (m, 2H), 3.65 (s, 3H), 3.52 (s, 2H), 2.82 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.55, 148.60, 139.08, 138.61, 137.46, 103.58, 92.25, 51.59, 50.97, 46.53, 44.79, 39.57; HRMS calcd for $C_{12}H_{16}ON_6Cl$ [M + H] 295.1074, found 295.1070.

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Notes

The authors declare no competing financial interest.

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(6) Compound **14** is stable as HCl salt. In free base form, it could dimerize or oligomerize as it has both amine and alkyl chloride in one molecule.

(7) The hydrogenation under improved condition was tested on 10 g scale. It has not been evaluated for large scale preparation.

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