Organic Process Research & Development

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Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/op5003769 • Publication Date (Web): 02 Jun 2015

Development of a Synthesis of a 2,3-Disubstituted-4,7-Diazaindole Including Large-Scale Application of $CH_3Li/TiCl_4$-Mediated Methylation of an Enolizable Ketone

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Abstract:

The chemical development of a 2,3-disubstituted-4,7-diazaindole is described. The requisite tertiary carbinol substrate was prepared employing *in situ*-generated CH_3TiCl_3 as a chemoselective and preferred reagent compared to CH_3MgX for methyl addition to an enolizable ketone. The 4,7-diazaindole ring system was efficiently assembled via an intramolecular Chichibabin transformation. The optimized processes were performed on pilot-plant scale to provide kilogram quantities of the target molecule.

Introduction

The original synthesis of **1** (Scheme 1), a compound under development as a Syk inhibitor,[1] suffered from several limitations. For example, 2-propylpyrazine (**4**) was prepared by alkylation of **2** with ethyl iodide under cryogenic reaction conditions. In addition, the isolation of **4** required a tedious fractional distillation in order to remove

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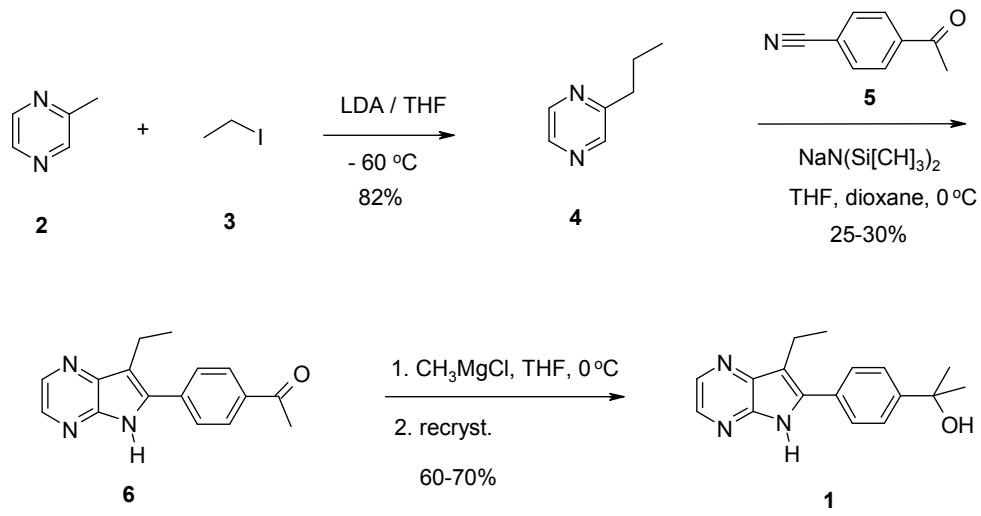
[1] Gillespy, T. A.; Eynott, P.; Allen, E. M.; Yu, K. T.; Zilberstein, A. *PCT Int. Appl.* US 2010/0035884 A1, 2010.

unreacted **2** and some 2-(pentan-3-yl)pyrazine side product that resulted from diethylation**,** both of which subsequently generated related impurities in downstream steps that were difficult to remove. Also, the reaction of the anion of **4** with the nitrile **5** and subsequent cyclization provided **6** in only about 25% yield. The overall yield of **1** was only about 12%. Consequently, in order to support the development program with multi-kg quantities of **1,** a more efficient and scalable synthesis was required.

Scheme 1. Original Synthesis of **1**



Results and Discussion

It was envisioned that the issues in the original route related to preparation of **4** could be mitigated by cross-coupling *n*-PrMgX with 2-chloropyrazine as described by Fürstner.[2] An initial probe of the iron-catalyzed cross-coupling method demonstrated feasibility and superiority over the original ethylation process, and was adapted to prepare early supplies of 2-propylpyrazine. The protocol consisted of adding 1.2 equiv of 1-propylmagnesium

[2] (a) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, 124, 13856. (b) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004***, 69*, 3943.

chloride to 2-chloropyrazine (**7**, Scheme 2) in the presence of 5 mol% $Fe(acac)_3$ at 10-25 ^oC over a 2-h period. Best conversions, achieving >97 area % (A%[3]) product, were obtained using THF as solvent compared to MTBE (77%), NMP/THF (4:1; 55%) and NMP:MTBE (1:1; 94%). The reaction was typically complete after stirring for an additional 10 min at 20 ^oC. Minor amounts of two side products were observed at <2% each, namely, pyrazine from dechlorination of the starting material and bipyrazine from a homocoupling pathway. After an aqueous quench, an extractive workup that included a wash with aqueous NaOH to remove 2,4-pentanedione derived from the catalyst, concentration, and simple distillation, **4** was obtained in 62-77% yield and >99.5% purity. This process was employed to prepare **4** used in pre-clinical manufacturing campaigns of **1**. As the project progressed, a bulk supplier emerged that was able to provide **4** from stock in >10-kg quantities and this material was utilized in subsequent manufacturing campaigns.

The reaction of the anion of **4** with a suitable aryl nitrile with subsequent intramolecular Chichibabin cyclization[4] was deemed to be a concise strategy for assembling the 4,7-diazaindole core structure in the target molecule. Complications in the original route (Scheme 1) were caused by enolate formation in two steps of the synthesis, namely, during the Chichibabin step and the Grignard methylation that led to poor conversions and the formation of aldol byproducts. An alternative approach that was envisioned to address enolate formation was reversing the Chichibabin and Grignard methylation sequences by methylating 4-acetylbenzonitrile prior to Chichibabin cyclization. In this approach, the

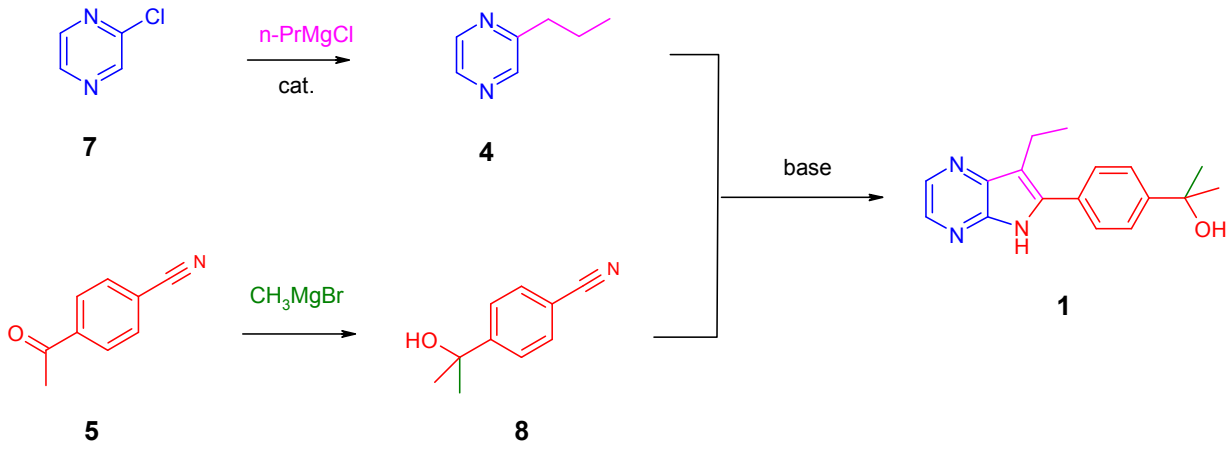
[3] All references to reaction conversion and purity are understood to be in terms of HPLC relative area % unless indicated otherwise.

[4] Vierfond, J.-M.; Mettey, Y.; Mascrier-Demagny, L.; Miocque, M. *Tetrahedron Lett.* **1981***, 22*, 1219.

ketone functionality would be present in only one step of the synthesis, and complications during the Chichibabin step from enolate formation of the methyl ketone would be eliminated.

Indeed, early lab results demonstrated feasibility and potential scalability for both the cross-coupling reaction to prepare **4** and the modified Chichibabin protocol, and this alternative, and now more convergent, route was selected for further development (Scheme 2).[5]

Scheme 2. Convergent Synthesis of **1**



Tertiary carbinol 8 prepared using CH_3MgX

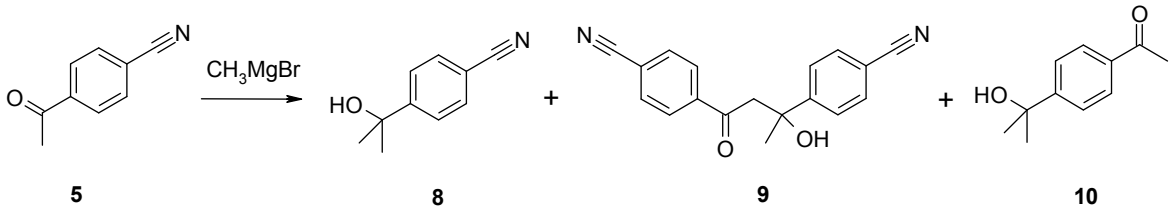
Initial supplies of 4-(1-hydroxy-1-methylethyl)benzonitrile (**8**) were prepared by methylation of 4-acetylbenzonitrile with 1.25 equiv of methylmagnesium bromide (3 M in diethyl ether) in methyl *tert*-butyl ether (MTBE) (Scheme 3).[6] Partial enolization of 4-acetylbenzonitrile caused by the basic methylmagnesium bromide resulted in incomplete consumption of starting material (2-15% remaining) and the formation of about 5-15% of

[5] Lee, G. E.; Shrimp II, F. L.; Weiberth, F. J. *PCT Int. Appl.* WO 2010/107969 A1, 2010.

[6] Popielarz, R.; Arnold, D. R. *J. Am. Chem. Soc.* **1990**, *112*, 3068.

the aldol side-product **9**.[7,8] The low solubility of the magnesium enolate of **5** in ether solvents, especially MTBE, prevented further conversions to **8** and limited the amounts of **9**. Similarly, the insolubility of the magnesium alkoxide of **8** contributed to achieving high chemoselectivity by minimizing over-reaction of the Grignard with the nitrile functionality to afford **10**.

Scheme 3. Reaction of **5** with CH_3MgBr



5 **8** **9** **10**

Typically, after 0.5 h at 10-15 °C following addition of Grignard reagent, the reaction slurry contained a 68:18:13 ratio of desired product : starting material : aldol product (compounds **8:5:9**) as determined by HPLC analysis. The addition of THF (3 V) facilitated some solubilization of the magnesium salts and further conversion of unreacted starting material to achieve a 79:8:13 ratio of **8:5:9**. After quench and an extractive workup, the resulting MTBE phase was then partially concentrated and filtered to remove some **9** that had crystallized to afford crude product as a concentrate containing a 89:5:5 ratio of **8:5:9**. Distillation through a short path column (1-2 mbar, 125-128 °C) followed by trituration with heptane, provided **8** as a white solid in 74-84% yield and >99% purity.

Although this preparation provided **8** in multi-kg quantities and in quality suitable for downstream chemistry, the protocol was tedious, especially the purification. The distillation of **8** to remove **5** in the forerun and **9** in the residue was not robust due to thermal dehydration of **8** to concomitantly form the corresponding styrene in small amounts. In some batches, perhaps due to variations in the quality of crude **8**, retro-aldol

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[7] ^{1}H NMR (300 MHz, $CHCl_3$, δ): 8.01 (d, *J* = 8.6 Hz, 2H), 7.79 (d, *J* = 8.6 Hz, 2H), 7.66-7.59 (m, 4H), 3.76 (d, *J* = 17.2 Hz, 1H), 3.52 (s, OH), 3.43 (d, *J* = 17.2 Hz, 1H), 1.65 (s, 3H).

[8] (a) Batchelor, K. J.; Bowman, W. R.; Davies, R. V.; Hockley, M. H.; Wilkins, D. J. *J. Chem Res.* **1999,** 428. (b) Tucker, J. L.; Couturier, M.; Leeman, K. R.; Hinderaker, M. P.; Andresen, B. M. *Org. Process Res. Dev.* **2003***, 7*, 929.

reaction of **9** was observed that contaminated fractions of **8** with **5** during the distillation. Screening experiments were performed that evaluated several reaction parameters, including reaction solvent, CH_3MgCl vs. CH_3MgBr, order of addition, and the temperature and duration of reagent addition. These studies did not identify conditions that could provide substantially improved conversions to **8**. The use of 10 mol% $ZnCl_2$ to suppress enolate formation[9] was not successful (>50% **9**). Adapting a report from Knochel[10] that described the beneficial effects of soluble lanthanide salts towards favoring the addition reaction over enolization, and using stoichiometric amounts of commercially available $LaCl_3 \cdot LiCl$ in THF with CH_3MgX, led to modest suppression of the aldol side product (5-10%). Alternative substrates were also considered. An oxidative protocol using *p*-cuminonitrile[11] was low yielding, and the aldol side reaction was still problematic when ester substrates[8] were employed.

Tertiary carbinol 8 prepared using CH_3TiCl_3

A search to identify a preferred methylating reagent that was a good nucleophile and a poor base as a means to retard or eliminate enolization led to an evaluation of CH_3TiCl_3,[12] previously described by Reetz.[13] Indeed, CH_3TiCl_3, prepared *in situ* from $TiCl_4$ and CH_3Li, was found to react chemoselectively with **5** without enolization to provide **8** as the sole product under optimized conditions (Scheme 4).

An attempt to replace CH_3Li with an analogous Grignard reagent was studied in several solvent systems, including, CPME, Bu_2O and *i*-Pr_2O. In general, the reaction of CH_3TiCl_3

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[9] (a) Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, *128*, 9998. (b) See also: Hatano, M.; Ito, O.; Suzuki, S.; Ishihara, K. *J. Org. Chem.* **2010**, *75*, 5008.

[10] Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem. Int. Ed.* **2006***, 45*, 497.

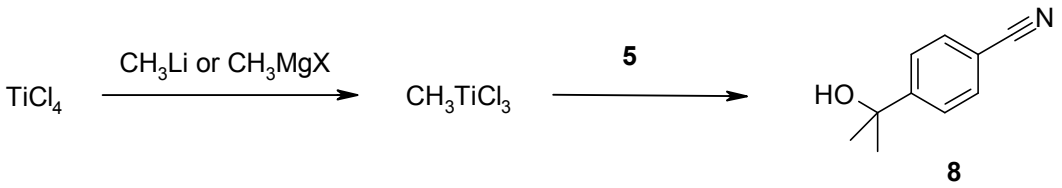
[11] Tucker, J. L.; Couturier, M.; Castaldi, M. J.; Chiu, C. K. F.; Gestmann, D. *Synth. Commun.* **2006***, 36*, 2145.

[12] For simplicity, this reagent is depicted as CH_3TiCl_3, although the actual species may be a solvate or another complex depending on the specific reaction conditions.

[13] Reetz, M. T.; Kyung, S. H.; Hüllmann, M. *Tetrahedron* **1986**, 42, 2931-2935. See also: Reetz, M. T. Organotitanium Chemistry. In *Organometallics in Synthesis*; Second Edition; Schlosser; M., Ed.; John Wiley & Sons, Ltd.: England, 2002; Chapter VII, pp. 819-860.

produced from $TiCl_4/CH_3MgBr$ [14] was less efficient than CH_3TiCl_3 produced from $TiCl_4/CH_3Li$. Reaction times were longer (20 h vs. 2 h) and conversions were incomplete (1-5% unreacted **5**), even when 3 equiv of the methylating reagent were employed.[15] Increases in the reaction time or temperature (25-30 ^oC) were detrimental, leading to only minor improvements in conversion while forming long-retention impurities. Consequently, efforts were focused on using CH_3TiCl_3 produced from $TiCl_4/CH_3Li$ rather than $TiCl_4/CH_3MgX$ based on better reaction performance and purity profile as the best balance versus the handling of CH_3Li on large scale.

Scheme 4. Methylation using CH_3TiCl_3



Several commercially available solution formulations of CH_3Li were evaluated and were found to be mainly equivalent in reaction performance, but with some differences in side reactions. CH_3TiCl_3 prepared from CH_3Li in ethyl ether (1.6 M) was not pursued beyond lab batches because of restrictions on handling diethyl ether on scale. CH_3TiCl_3 prepared from CH_3Li in diethoxymethane (3 M) performed well in the methylation. But, upon quenching of the reaction at -2 to 6 ^oC, about 6% of the mixed acetal **11** formed (Scheme 5). Although this impurity could be avoided (<0.1%) by quenching at < -15 ^oC, there was an additional concern that acid generated during workup may produce formaldehyde, a genotoxin, from diethoxymethane. CH_3TiCl_3 prepared from CH_3Li in cumene/2-MeTHF[16] also performed well in spite of the presence of two lithiated cumene impurities present at levels <1 mol% in the commercial CH_3Li solutions. These reactive impurities led to the

[14] For an analogous application employing $CeCl_3/CH_3MgCl$, including pretreatment and activation of $CeCl_3$, see Larkin, J. P.; Wehrey, C.; Boffelli, P.; Lagraulet, H.; Lemaitre, G.; Nedelec, A,; Prat, D. *Org. Process Res. Dev.* **2002***, 6*, 20, and related references cited therein.

[15] Typically 1-5% unreacted **5** remained after more than 20 h at 20 ^oC.

[16] Typically, 2.5-3.5 wt% CH_3Li, 12-16 wt% 2-MeTHF, <2 wt% heptane, with cumene making up the balance.

formation of about 1.5% of the corresponding addition products **12** and **13** when the methylations were performed at 20 °C (Scheme 6), but their levels were minimized (<0.1%) by performing the methylations at -10 to 0 °C. In case further mitigations were needed, it was demonstrated that both **12** and **13** were readily purged into the filtrate during isolation of **8**. Reaction performance using CH_3Li in cumene/THF was equivalent to the cumene/2-MeTHF formulation, including the generation and control of impurities **12** and **13**, but there were supply chain issues and higher pricing for bulk quantities at the time for this reagent formulation. As result, CH_3Li in cumene/2-MeTHF was selected as the preferred reagent for further development.

Scheme 5. Formation of mixed acetal **11**

8 **11**

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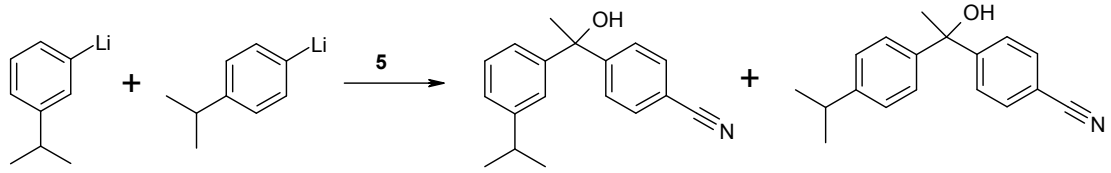
Scheme 6. **Addition products from metalated impurities in CH_3Li**



12 **13**

The effects of various ether solvents and other parameters, including stoichiometry, reaction time and temperature, on methylation using CH_3TiCl_3 generated from equimolar quantities of $TiCl_4$ and CH_3Li, were studied, and the results are summarized in Table 1. Cryogenic temperatures were not necessary. The reagent was prepared by treating $TiCl_4$ with CH_3Li at 0 to -10 °C. Then, after aging for about 30 min at -5 °C, **5** was added. The aldol side reaction was observed when the methylation was performed in 2-MeTHF, THF and 1,2-dimethoxyethane. The methylation was sluggish in MTBE. CPME and anisole were the best solvents. About 1.5 equiv of CH_3TiCl_3 were needed for complete reaction of **5**. The methylation was best performed at -10 to 0 °C to avoid the formation of the cumenyl side products observed when the reaction was performed at 20 °C (Entry 13).

Anisole was selected as the preferred solvent for the transformation despite the anticipated use of CPME in the next step of the synthesis because of limited commercial supplies and the relatively high cost of CPME. Methylation was complete (<0.3 of **5**) after stirring at -5 °C for 0.5-1 h. The reaction was quenched by the addition of water over a period of 45 min to control the exotherm and evolution of methane.[17] After an extractive workup, the anisole was removed[18] azeotropically using water added in several portions. After a solvent swap, the product was crystallized from cumene/heptane to give **8** as a white crystalline solid in 81-85% yield on pilot-plant scale, with 100% purity by HPLC assay and containing <5 ppm residual Ti and <1 ppm residual Li.

Table 1: Methylation of 5 using *in situ*-generated CH_3TiCl_3 from $TiCl_4$ and CH_3Li

Entry	CH_3TiCl_3[a] equiv	Solvent[b]	Temp °C	Time h	Product 8 A%[c]	Unreacted 5 A%	Aldol Diol[d] A%
1	1.3	CPME	-3 to 9	6	98.2	0.6	0
2	1.5	CPME	0 to -3	3	98.6	0.3	0
3	1.5	2-MeTHF	-5 to 8	16	88.0	4.0	5.1
4	2.0	MTBE	-5 to 8	9	76.2	21.1	0
5	1.5	Bu_2O	-1 to 7	7	21.5	77.7	0
6	1.5	DME	-7 to 9	7	73.2	16.9	2.8
7	1.5	THF	6 to -7	7	46.1	32.8	13.3
8	1.5	*i*-Pr_2O	1 to -4	5	97.7	1.0	0
9	2.0	*i*-Pr_2O	0 to -4	2	99.5	0.2	0
10	1.1	anisole	-7 to -10	4	94.2	5.8	0
11	1.2	anisole	-3 to -5	2	99.3	0.7	0
12	1.5	anisole	-4 to -5	1	99.7	0.3	0
13	1.5	anisole	20-21	1	97.8[e]	0	0

[a] CH_3TiCl_3 formed at -5 to -10 °C from equimolar quantities of $TiCl_4$ and CH_3Li; [b] Typically 10 V; [c] Area % by HPLC analysis. [d] Diol from methylation of aldol by-product **9**. [e] Plus 1.3% of cuminyl impurities **12**/**13** and 0.6% of other impurities.

[17] Alternatively, excess reagent can be quenched using acetone without methane evolution.

[18] The carbinol **8** is highly soluble in anisole and in ether solvents in general. Attempts to isolate **8** from anisole in high recovery by direct crystallization were not successful.

Intramolecular Chichibabin cyclization

It had been known from prior experiences with synthesizing diazaindoles for related chemical series that HMDS bases and LDA would be preferred bases to prepare **1** via an intramolecular Chichibabin protocol.[19] At least three equivalents of base were required for the overall transformation, namely, to produce the alkoxide of **8**, generate the benzylic anion of **4** for reaction at the nitrile, and then to regenerate the anion at the benzylic position to effect the cyclization.[20] KHMDS generally gave the best conversions. NaHMDS had lower conversions even at longer reaction times. LiHMDS and LDA both gave sluggish reactions and produced >6% of the uncyclized enamine **16**.

The highest conversions were obtained when the reaction was performed in ether solvents. The initial two batches in a 1-kg campaign of **1** employed solid KHMDS (4 equiv) in MTBE and 1.5 equiv of 2-propylpyrazine at 20-25 °C to give isolated yields of 55% and 72% of crude **1** after 24 h and 120 h, respectively. The time-dependent increase in yield was attributed to a partially reversible formation of benzamidine **14,** an adduct derived from **8** and KHMDS, likely as a sterically hindered mono- or bis-trimethylsilylated form preventing trimerization to the s-triazine. A maximum formation of 30% of **14** was observed after 24 h that decreased to 18% after five days with a corresponding increase in the formation of **1**. The reaction conversion and isolation was facilitated by the insolubility of the product. Thus, **1** was obtained in 72% yield in >97.5% purity by HPLC analysis after simply diluting the reaction suspension with water and filtering.

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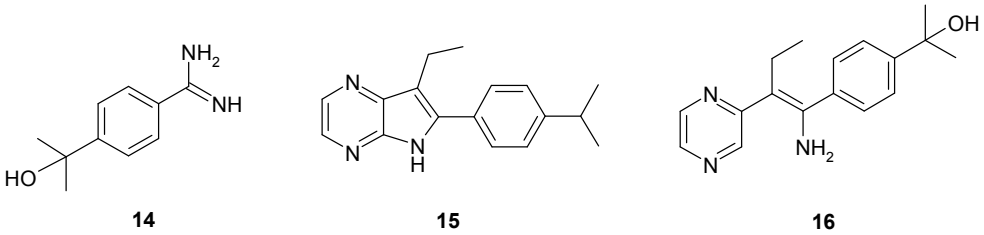
[19] Astolfi, D.; Ayers, T. A.; Chandramouli, S. V.; Hillegass, A.; Kubiak, G. G.; Lee, G. E.; Lythgoe, D. J.; Powers, M. R.; Subotkowski, W.; Vanasse, B.; Weiberth, F. J.; Yu, Y. *PCT Int. Appl.* WO 2008/014249 A2, 2008.

[20] For insights on the reaction mechanism, see ref. 2 and (a) Davis, M. L.; Wakefield, B. J.; Wardell, J. A. *Tetrahedron* **1992***, 48*, 939. (b) McGill, C. K.; Rappa, A. *Adv. Heterocycl. Chem.* **1988***, 44*, 1.

Fig. 1. Side products.



14 **15** **16**

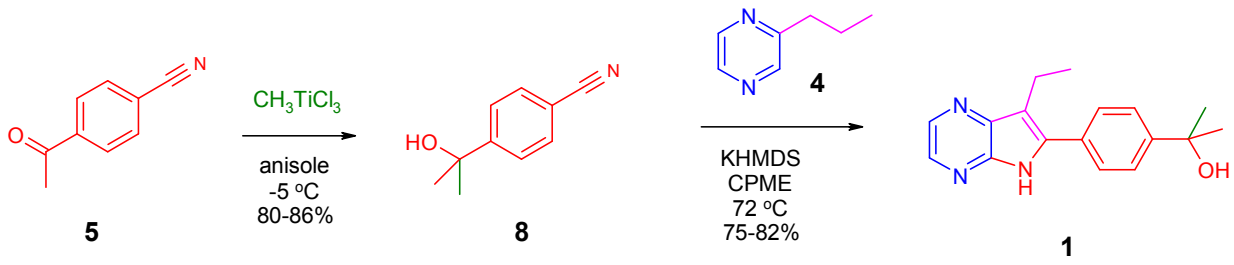
Because the solid KHMDS that was used in initial campaigns was found to have inconsistent quality between lots and limited availability, the use of commercially available KHMDS as a 19 wt% solution in THF was evaluated. Unfortunately, unacceptable levels (4-8%) of the isopropyl side product **15** were formed in reactions performed in THF, MeTHF, or alternative solvents that became enriched with THF that was contributed from the KHMDS/THF reagent. The extent of the formation of **15** from **1** was a function of the solubility of **1** in the solvent system together with reaction temperature and reaction time. A mitigating strategy that was successful in minimizing the formation of **15** was employing CPME as a co-solvent and reducing the amount of THF in commercial KHMDS/THF to acceptable performance levels (<5 wt%) by co-distillation prior to reaction. Thus, CPME emerged as the preferred solvent for the cyclization, and ultimately, a sourcing partner was developed that was able to supply bulk quantities of KHMDS as a 32 wt% solution in CPME.

Further efforts to refine the Chichibabin cyclization centered on optimizing reaction temperature, equivalents of **4** and equivalents of base. Yields improved to 87% by increasing the reaction temperature from 20 ºC to 75 ºC likely because of a shift in the amidine ↔ nitrile equilibrium favoring nitrile as temperature increased followed by irreversible conversion of reformed nitrile to **1**. At higher temperatures, an added benefit was a decrease in reaction time from 24 h to 5 h. Employing 1.25 equiv of **4** was slightly beneficial compared to using 1.1 equiv (87% vs. 83%). In a series of experiments using 1.25 equiv of 2-propylpyrazine and comparing reaction performance at 70 ^{o}C using 3.1, 3.25, 3.5 and 4.0 equiv of KHMDS in CPME, **1** was obtained in 77, 81, 84 and 87% isolated yield, respectively, after 5 h at 70 ºC. Temperatures much above 75 ºC were avoided in order to minimize formation of the isopropyl side product **15**. These parameters

were successfully scaled in a pilot plant using 162.5 moles of **8**, 1.25 equiv of **4**, and 4.0 equiv of KHMDS in CPME. The reaction was complete after 6 h at 70-75 °C. After cooling, quenching with water, filtering and drying, **1** was obtained as light-yellow solid in 81% yield.

In summary, the chemical development of a 2,3-disubstituted-4,7-diazaindole has been described. The tertiary carbinol **8** was prepared employing *in situ*-generated CH_3TiCl_3 as a preferred reagent compared to CH_3MgX for methyl addition to an enolizable ketone. The 4,7-diazaindole ring system was efficiently assembled via an intramolecular Chichibabin transformation. The optimized processes were performed on pilot-plant scale to provide 72 kg of **1** in two campaigns in 60-68% overall yield.

Scheme 7. Final Synthesis



Experimental Section

*Preparation of 4-(1-hydroxy-1-methylethyl)benzonitrile (**8**).*

A reactor containing anisole (85 kg) was cooled to -10 to -5 °C. $TiCl_4$ (17 kg, 89.6 mol, 1.5 equiv) was charged over 1 h while maintaining -10 to -5 °C. After stirring at -10 to -5 °C for 15 min, an orange suspension was obtained. A solution of CH_3Li in cumene/2-MeTHF (61 kg, 3.2 wt%, 88.9 mol, 1.5 equiv) was charged over 100 min at -10 to -5 °C. The reddish solution was stirred at -10 to -5 °C for 35 min. A solution of **5** (8.5 kg, 58.6 mol) in anisole (43 kg) was added over 80 min at -10 to -2 °C. The reddish solution was stirred at -5 to -2 °C for 60 min. HPLC analysis of an in-process sample indicated that the reaction was complete (<0.5% **5**). The reaction was quenched by the addition of water[17,21] (4.3 kg) over 30 min at -10 to 0 °C. The reaction was partitioned by adding water (38 kg), and was then warmed to 18 °C. The organic phase was separated, and then washed with water (2 x 43 kg), aqueous $NaHCO_3$ (8% w/v, 2 x 110 kg) and water (2 x 43 kg). Anisole was removed as an azeotrope with water (total 255 kg water added over five portions as the reactor volume allowed) by distillation (45-50 Torr, <55 °C internal temperature). The resulting mixture, comprised of crude product as an organic phase (containing <0.5% anisole by GC analysis) and a water phase, was diluted with cumene (22 kg), MTBE (31 kg) and aq NaCl (25 wt%, 20 kg), and then separated. The organic phase was then partially concentrated (70-75 Torr, <60 °C internal temperature) to remove MTBE until a volume of about 30 L was achieved. The organic layer was filtered (0.8 μ cartridge) to remove extraneous solids. The filtrate was heated to 65-70 °C and heptane (5.8 kg) was added. The clear solution was cooled to 20 °C and seeded with pure **8** (8.5 g). Crystallization commenced within 5 min exothermically (temperature rose to 23 °C in 20 min). The suspension was stirred at 20-22 °C for 2 h, and then heptane (29 kg) was added over a 60-min period. The suspension was stirred at 20-22 °C for 1 h, cooled and aged at 0-5 °C for 3 h, and was then filtered. The cake was washed with cumene/heptane (8.5 kg:0.5 kg) and heptane (8.5 kg) and then dried under reduced pressure at 35 °C to afford

[21] Gas evolution was vigorous during the initial part of the quench.

8.0 kg (84% yield, 100% purity[22]) of **8** as a white crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$): 1.58 (s, 6H), 1.85 (s, 1H), 7.45-7.55 (m, 4H).

*Preparation of 2-[4-(7-ethyl-5H-pyrrolo[2,3b]pyrazin-6-yl)phenyl]propan-2-ol (**1**)*

A reactor was charged with **8** (26.2 kg, 162.5 mol), 2-propylpyrazine (25.0 kg, 204.6 mol, 1.25 equiv) and CPME (180 kg). Potassium bis(trimethylsilyl)amide (410 kg of 32 wt% solution in CPME, 657 mol, 4 equiv) was added over 70 min while allowing the temperature to rise to about 35 °C. The batch was heated and held at 70-76 °C for 6 h. The suspension was cooled to 22 °C over 1 h. Water (81 kg) was added in 45 min while maintaining <45 °C. The thick suspension was stirred for 35 min, cooled and aged at 5 °C for 1.5 h, and then was transferred to a filter followed by CPME/water rinse (41:7 kg). The cake was washed with water/MeOH (580 kg/200 kg) followed by water (to pH < 12), and was then dried at 70 °C to afford **1** as a light-yellow solid (37.3 kg, 132.5 mol, 81.6% yield, 99.6% purity[23]). ^{1}H NMR (300 MHz, DMSO-d_6): 1.29 (t, J = 7.4 Hz, 3H), 1.48 (s, 6H), 2.92 (q, J = 7.5 Hz, 2H), 5.12 (s, 1H), 7.64 (s, 4H), 8.20 (d, J = 2.6 Hz, 1H), 8.35 (d, J = 2.6 Hz, 1H). 12.03 (br s, 1H)

Acknowledgements

We gratefully acknowledge Andrew Bridge, David Lythgoe and Michel Mulhauser for their encouragement and helpful discussions, and Geoffrey Darnbrough, Anthony Gardetto, Matthew Powers, Laura Turci, Benoit Vanasse and other colleagues within our organization who provided process safety, analytical, sourcing and pilot plant operations support.

[22] Zorbax Eclipse XDB-C8, 4.6 x 150 mm, 5 µ, 240 nm, 25 °C, water/ACN/TFA, 1 mL/min, gradient program: 70/30/0.1 for 10 min, then linear ramp over 5 min to 15/85/0.1, then held for 5 min. Relative retention times: **8**, 1.00; **5**, 1.33.

[23] Zorbax Eclipse XDB-C8, 4.6 x 150 mm, 5 µ, 250 nm, 35 °C, 40:60:0.1 water/ACN/TFA isocratic, 1 mL/min for 20 min. Relative retention times: **1**, 1.00; **8**, 1.23.

Development of a Synthesis of a 2,3-Disubstituted-4,7-Diazaindole Including Large-Scale Application of $CH_3Li/TiCl_4$-Mediated Methylation of an Enolizable Ketone

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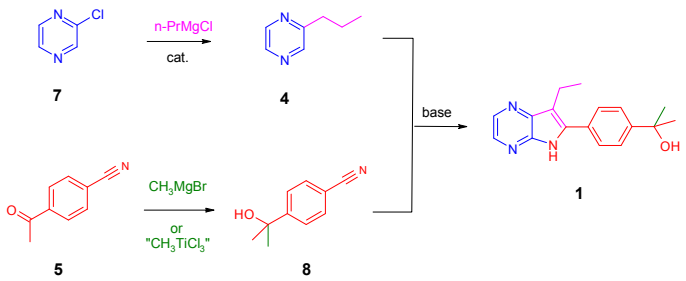

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