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Regioselective synthesis of 4-(2-alkyl-5-methyl-2*H*-pyrazol-3-yl)-piperidines

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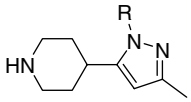
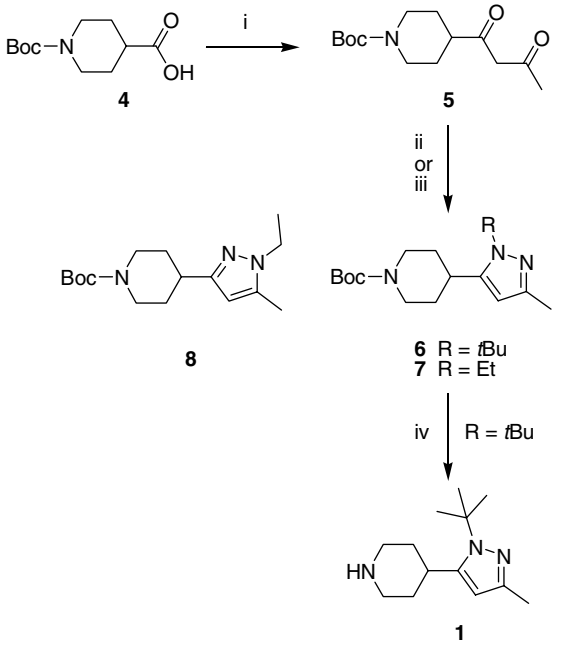
Abstract—The regioselective, scaleable synthesis of three 4-(2-alkyl-5-methyl-2*H*-pyrazol-3-yl)-piperidines is discussed.

The 4-(pyrazolyl)piperidine unit is a ubiquitous constituent of biologically active compounds. As part of a medicinal chemistry program, we required an efficient, practical and scaleable synthesis of the 4-(pyrazolyl)piperidines **1**, **2** and **3**. While there are many reports of substituted pyrazole syntheses,[1] regioselective routes to 4-(pyrazolyl)piperidines are scarce and usually not amenable to large-scale synthesis.[2] Herein we report practical, regioselective and scaleable syntheses of **1**, **2** and **3**.



1 R = *t*Bu
2 R = Et
3 R = CH_2CF_3

Our initial route (Scheme 1) starts from the commercially available *N*-Boc-isonipecotic acid **4**, which is converted to diketone **5** using the potassium enolate of acetone. Condensation of *tert*-butyl hydrazine yields pyrazole **6** as a single regioisomer[3] in 90% yield. Compound **1** was obtained after deprotection using acetyl chloride in methanol, and is purified by recrystallisation from 2-propanol. This sequence does not require chromatographic purification at any stage and has been carried out on 100 g batches.



Scheme 1. Reagents and conditions: (i) CDI, DCM, then acetone, KH, THF, −78 °C, 99%; (ii) *t*BuNHNH$_2$·HCl, Et$_3$N, EtOH, rt, 90%; (iii) EtNHNH$_2$·oxalate, Et$_3$N, EtOH, rt, 90%, **7**/**8**: 1:1; (iv) AcCl, MeOH, rt, 99%.

Condensation of ethyl hydrazine onto **5** produces a 1/1 mixture of regioisomers **7** and **8**.[4] Although feasible on a 20 g scale, chromatographic separation of **7** from **8** is problematic and this route is impractical on a larger scale.[5] This is also true for the synthesis of **3**, even

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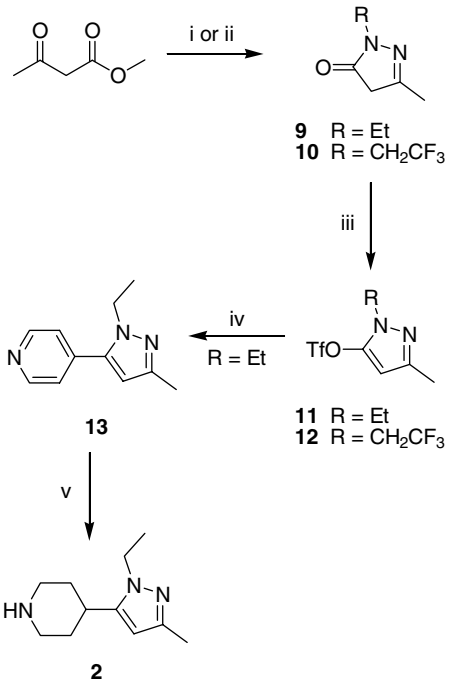
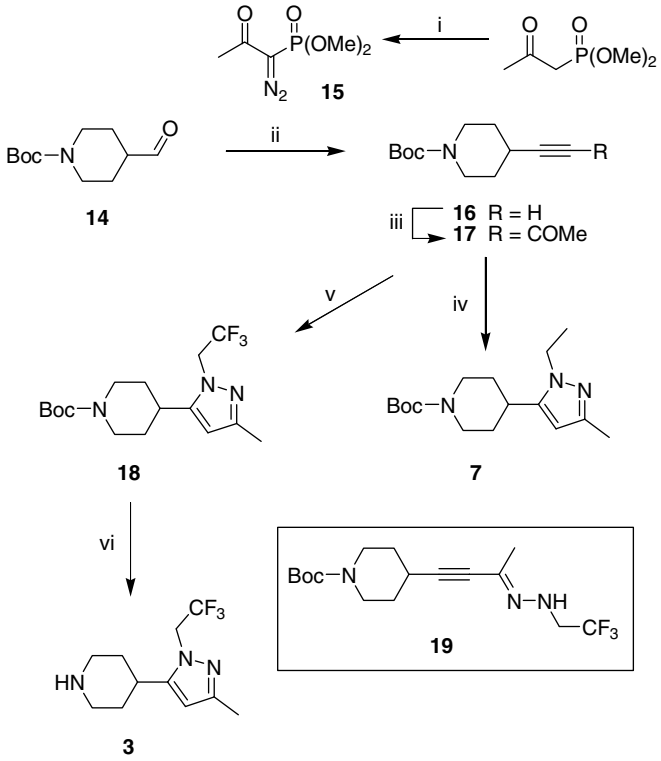


Scheme 2. Reagents and conditions: (i) $EtNHNH_2$·oxalate, Et_3N, EtOH, rt to 60 °C, 99%; (ii) $CF_3CH_2NHNH_2$, EtOH, rt to 60 °C, 99%; (iii) $PhNTf_2$, DIPEA, DCM, Δ, 80%; (iv) 4-pyridyl boronic acid, K_3PO_4, $PdCl_2$dppf, dppf, 1,4-dioxane, 100 °C, 70%; (v) H_2 (50 psi), PtO_2, HCl, EtOH, rt, 90%.

though here the hydrazine condensation yields a 5/1 mixture of pyrazoles in favour of the desired isomer.

We therefore sought a new regioselective synthesis of **2** and **3**. Recently, Dvorak et al. reported a general protocol for the palladium-mediated Suzuki coupling reaction of pyrazole triflates and aryl boronic acids.[1d] We hypothesised that if 4-pyridyl boronic acid was a competent partner in this reaction, this chemistry could be used to yield a regioselective route to the desired piperidines after reduction of the pyridine ring. The realisation of the approach is shown in Scheme 2. Ethyl and trifluoroethyl pyrazolones **9** and **10** can be very efficiently prepared by condensation of the required hydrazine onto the inexpensive methyl acetoacetate. Alternatively, methyl tetrolate can be used instead of methyl acetoacetate with equal effectiveness. The formation of the triflates **11** and **12** proceeds smoothly using *N*-phenyl bis-triflamide and Hünig's base in refluxing dichloromethane. Gratifyingly, the palladium catalysed cross coupling of **11** with 4-pyridyl boronic acid yielded the desired pyridine pyrazole in 70% yield. This reaction appeared to be very sensitive to concentration (0.15 M optimum) and catalyst loading (8 mol % palladium and 4 mol % dppf). The completion of the synthesis of **2** was achieved in high yield after hydrogenation in acidic media using platinum oxide as a catalyst. A final recrystallisation of the hydrochloride salt from 2-propanol delivers **2** in pure form. In this way, **2** has been synthesised in four steps with total regioselectivity in 50% yield from inexpensive starting materials. This sequence has been successfully carried out on 100 g batches.

Unfortunately, all attempts to couple **12** with 4-pyridyl boronic acid were unsuccessful. We therefore had to



Scheme 3. Reagents and conditions: (i) 4-acetamidobenzenesulfonyl azide, NaH, THF, PhMe, 0 °C, 98%; (ii) **15**, K_2CO_3, MeOH, rt, 81%; (iii) *n*BuLi, MeCON(OMe)Me, THF, −78 °C, 85%; (iv) $EtNHNH_2$·oxalate, Et_3N, EtOH, rt to 60 °C, 50%, **7/8**: 12:1; (v) $CF_3CH_2NHNH_2$, AcOH, EtOH, MW 150 °C, 3 h, 72%; (vi) AcCl, MeOH, rt, 95%.

develop another route for a practical synthesis of **3**. An alternative regioselective synthesis is shown in Scheme 3 using an ynone as the coupling partner for the alkylhydrazine. The commercial aldehyde **14** was converted into alkyne **16** using the Bestmann reagent **15** in good yield.[6] The preparation of the Bestmann reagent normally requires two steps from readily available starting materials, as tosyl azide is no longer commercially available. We report here a true one-step procedure to prepare the Bestmann reagent, using 4-acetamidobenzenesulfonyl azide as the diazo transfer agent.[7] This azide has the advantage of being less hazardous than tosyl azide, and we prepared >150 g batches of the Bestmann reagent using this protocol. Ynone **17** is obtained by alkylation of **16** using *N*-methoxy-*N*-methylacetamide. Addition of ethyl hydrazine to **17** at 60 °C yields a 12/1 mixture of regioisomeric pyrazoles **7** and **8** in favour of the desired isomer **7**. The addition of trifluoroethyl hydrazine requires more forcing conditions to produce the desired pyrazole directly, as hydrazone **19** is isolated as the major product after heating at 60 °C.[8] After optimisation, we found that acetic acid was needed (presumably to facilitate the trans to cis isomerisation of the kinetically formed hydrazone **19**), and the optimal temperature profile was three hour microwave[9] heating at 150 °C; higher temperatures result in loss of the Boc protecting group, and lower temperatures yield mostly hydrazone **19**. Gratifyingly, these conditions produce **18** as a 13/1 mixture of regioisomers in 72% isolated yield. A final deprotection and recrystallisation from 2-propanol gave the desired pyrazole **3** in good yield and purity. This third route allows a practical, regioselective synthesis of **3**, and a rapid access to diversely 2,5-disubstituted pyrazole piperidines in three steps from alkyne **16** using the appropriate Weinreb amide and hydrazine combination.

In conclusion, we have developed scaleable and practical routes to the 4-(pyrazolyl)-piperidines **1**, **2** and **3**. The synthesis of **1** relies on a regioselective addition of *tert*-butyl hydrazine onto a 1,3-diketone. This high selectivity is not observed when ethyl or trifluoroethyl hydrazines are used. Alternatively, a Suzuki coupling between a pyrazole triflate and 4-pyridyl boronic acid allows the regioselective synthesis of **2** in excellent yield. Finally, a more flexible route allowing rapid synthesis of diversely 2,5-disubstituted pyrazole piperidines has been described using a regioselective addition of an alkylhydrazine to an ynone as the key step. This route allowed a practical large-scale synthesis of **3**.

References and notes

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3. By ^{1}H NMR. ^{1}H NMR (360 MHz, CD_3OD): δ 5.97 (s, 1 H); 3.18–3.08 (m, 3H); 2.72–2.64 (m, 2H); 2.15 (s, 3H); 1.82 (m, 2H); 1.61 (m, 11H); 1.45 (s, 9H).
4. Structure of **7** and **8** assigned by NOE experiments.
5. Separation of the regioisomers proved impossible by crystallisation at any stage of the sequence.
6. Roth, G. J.; Liepold, B.; Mueller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59.
7. Dimethyl (2-oxopropyl)phosphonate (50 g, 0.30 mol), THF (270 mL) and toluene (1.3 L) were charged to a reaction vessel with stirring under nitrogen. Ice cooling was applied, and sodium hydride (60% in mineral oil) (13.25 g, 0.33 mol) was added over 10 min. The turbid yellow mixture was stirred for one hour with ice water cooling. 4-Acetamidobenzenesulfonyl azide (80 g, 0.33 mol) was then added over 10 min. The turbid orange mixture was stirred overnight at room temperature under nitrogen. The orange mixture was filtered on a Celite pad, the resulting cake was washed with toluene (250 mL), EtOAc (500 mL) and the filtrate was concentrated in vacuo. Compound **16** (57 g) was isolated pure as a clear liquid after a filtration on silica gel (EtOAc) in 98% yield.
8. When the hydrazine addition is performed at 60 °C, hydrazone **19** is isolated in 50% yield, alongside less than 10% of pyrazole **18**. A variety of acidic and basic conditions were screened to transform **19** into the pyrazole **18** presumably through a trans to cis isomerisation of the hydrazone. Three equivalents of acetic acid in refluxing ethanol gave the best reaction profile (with fewer side products), yielding **18** as a single regioisomer in 25% yield.
9. Microwave heating performed in a SmithSynthesizer in 20 mL vials.