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A Convenient Synthesis of Highly Substituted 2-Pyridones

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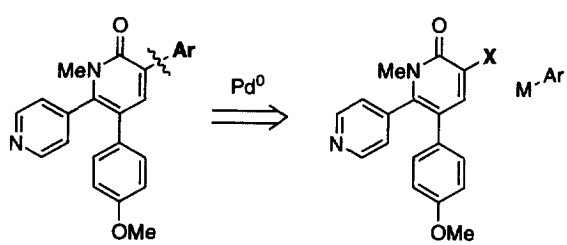
Abstract: A rapid and convenient synthesis of the 3-trifluoromethanesulfonyloxy-2-pyridone **2**, one of the first examples of this class of compound, was achieved by Vilsmeier formylation and cyclisation of the acyl enamine **6**. The triflate **2** was found to undergo a range of palladium-catalysed coupling reactions giving a synthetic sequence of general use for the preparation of highly substituted 2-pyridones.

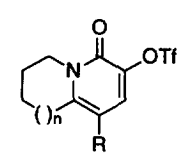
Key words: Pyridones; Coupling reactions; Vilsmeier reactions/reagents

Substituted monocyclic 2-pyridones are an important class of biologically active compounds which have widespread pharmaceutical use including analgesic, hypnotic, antifungal and cardiotonic actions.[1] Recently we identified the 2-pyridones **1**[2] (**Figure 1**) and related compounds[3] as selective ligands for the benzodiazepine binding site of GABA-A receptors with potential application as anxiolytics with improved side-effect profiles. In connection with this work we sought a rapid and efficient synthetic route to explore the structure–activity relationships of compounds such as **1**, especially by variation of the 3-substituent. The disconnection shown in Figure 1 was particularly attractive, and was envisaged to arise from palladium mediated cross-coupling reactions to the novel 3-trifluoromethanesulfonyloxy-2-pyridone **2**. This communication describes the successful formylation-cyclisation of an acyl enamine to give the triflate **2** and the subsequent cross-coupling chemistry that was achieved with this intermediate, providing a convenient, convergent and general route to highly functionalised pyridones of biological interest.



1 **2** X = OTf

Figure 1



n = 0, R = SO_2Ph
n = 1, R = CO_2Me

3

Figure 2

At the outset of this work we were unable to find examples of transition metal mediated couplings to 3-trifluoromethanesulfonyloxy-2-pyridones. Recently the syntheses, Stille cross-couplings and reductions of the bicyclic pyridone 3-triflates **3** (**Figure 2**) were reported by Padwa *et al.*[4] The synthesis and reactivity of 4-

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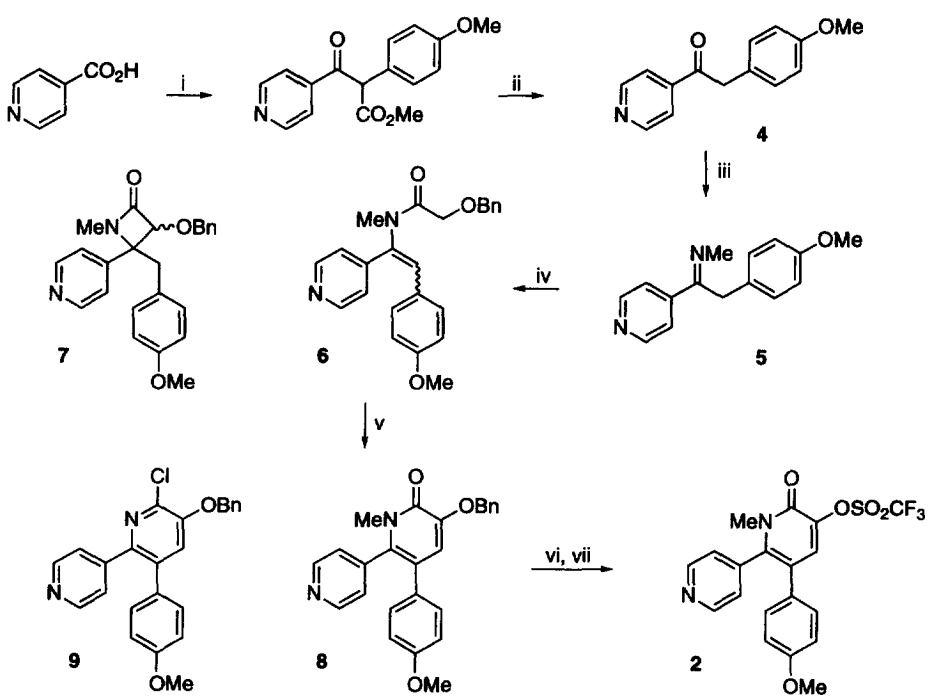
trifluoromethanesulfonyloxy-2-pyridones have been investigated,[5] but there are few reports concerning 5-trifluoromethanesulfonyloxy-2-pyridones[6] which have now been used in a novel synthesis of tricyclic pyridone GABA-A ligands.[7]

The key triflate intermediate **2** was prepared by the formylation-cyclisation of an appropriately substituted acyl enamine using the Vilsmeier reagent[8] (**Scheme 1**). This method had been applied to the synthesis of alkyl substituted 2-pyridones and was known to be effective for the introduction of a phenoxy group at the 3-position of the heterocycle.[9] Claisen condensation of isonicotinic acid, activated as the imidazolide, with the enolate of methyl 4-methoxyphenylacetate was followed by decarboxylation under Krapcho conditions[10] to yield the ketone **4**. This was converted to the *N*-methyl imine **5** upon treatment with methylamine and titanium tetrachloride.[11] The crude imine was acylated with benzyloxyacetyl chloride[12] to provide the desired acyl enamine **6** in good yield (59%) accompanied by small amounts (≤10%) of the β-lactam **7**, presumably as a result of competing ketene formation through elimination of the acid chloride and subsequent [2+2] cycloaddition to the imine. Indeed, if an equivalent of triethylamine was included in the acylation reaction, a 1:1 mixture of **6**:**7** was obtained (80%). Nevertheless, the required acyl enamine could be reliably prepared on multigram scale by this procedure.

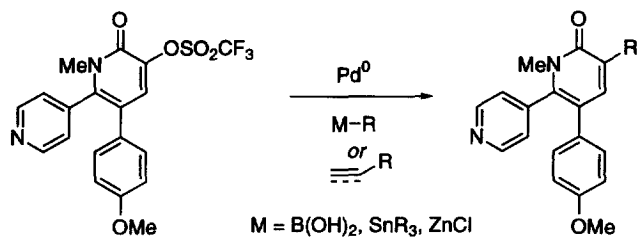


Reagents and conditions: i) N,N'-carbonyldiimidazole, DMF, rt *then* methyl 4-methoxyphenylacetate, NaH, rt (45%); ii) NaCl, H_2O, DMSO, 150°C (87%); iii) $MeNH_2$, $TiCl_4$, $CHCl_3$, 0°C; iv) $ClOCCH_2OBn$, THF, 0°C (59%, two steps); v) $POCl_3$, DMF, 0–75°C *then* H_2O, 0°C (48%); vi) Pd-C, HCO_2NH_4, AcOH, MeOH, rt (75%); vii) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, -78–0°C (90%)

Scheme 1

Treatment of **6** with $POCl_3$–DMF at elevated temperature[9] gave a 1-methyl-2-chloropyridinium

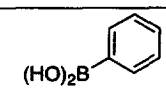
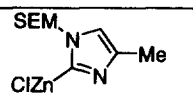
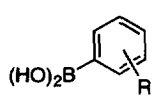
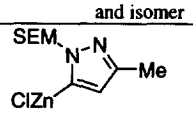
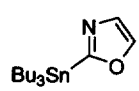
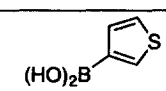
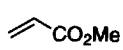
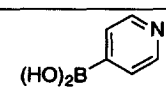
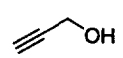
species[13] whose presence could be inferred from analysis of the reaction mixture by electrospray mass spectrometry. Following hydrolysis of this material, the 2-pyridone **8** was isolated in fair yield (48%), accompanied by the chloropyridine **9** (*ca.* 5-10%), the result of demethylation of the intermediate pyridinium salt. The benzyl protecting group was removed by catalytic transfer hydrogenolysis and the 3-hydroxy-2-pyridone was converted in excellent yield to the triflate **2** under standard conditions. This route served to produce several grams of the triflate **2**, which did not significantly degrade upon storage at room temperature over several months.



2 **1**

Scheme 2

Table 1

No.	Method[a]	M–R	Yield[b] (%)	No.	Method[a]	M–R	Yield[b] (%)
1	A		61	12[c]	B	 and isomer	51
2	A	 2-OMe	63	13[c]	B	 and isomer	28
3		3-OMe	70				
4		4-OMe	41				
5		4-Cl	36				
6		4-F	47				
7		4-CF_3	21				
8		3-NH_2	61	14[d]	C		44
9		3-NO_2	29				
10	A		67	15	D		41
11	A		69	16	E		27

[a]Method A: $Pd(PPh_3)_4$, Na_2CO_3, DME-H_2O, 100°C; Method B: $Pd(PPh_3)_4$, THF, 50°C; Method C: $Pd(PPh_3)_4$, DMF, 100°C; Method D: $Pd(OAc)_2$, PPh_3, LiCl, Et_3N, 100°C; Method E: $Pd(PPh_3)_4$, CuI, Et_3N, 100°C. [b]Isolated yields (unoptimised) of final compounds with purity of 95-99% as measured by hplc. [c]Organozinc formed by deprotonation of a mixture of the regioisomeric protected heterocycle with Bu^nLi and transmetalation with $ZnCl_2$ (ref. 17). The major isomer is shown. [d]ref. 19.

A range of palladium-catalysed couplings to **2** were examined (**Scheme 2** and **Table 1**). In most cases commercial *tetrakis*(triphenylphosphine)palladium was an effective catalyst and no further optimisation of the conditions or catalyst mixture was attempted. Both electron-rich and electron-poor arylboronic acids were

coupled to the triflate **2** (entries 1–11) under Suzuki conditions[14] and these reactions were conveniently carried out in parallel in batches of 5-12 compounds.[15]

Other heterocycles were introduced by Negishi coupling[16] of the organozinc halides[17] (entries 12, 13). For the SEM-protected imidazole and pyrazole, the protecting group was removed after coupling by acid treatment (5M HCl, 60°C, 47% and 53% yield respectively). Stille coupling[18] of a heterocyclic stannane[19] to the triflate **2** was also effective (entry 14) and the successful Heck[20] and Sonogashira[21] reactions (entries 15, 16) further demonstrated the versatility of this intermediate. The biological activity of the target compounds **1** will be reported in due course.[22]

In summary, a rapid and convenient synthesis of the 3-trifluoromethanesulfonyloxy-2-pyridone **2**, one of the first examples of this class of compound, was achieved by formylation-cyclisation of the acyl enamine **6**. The triflate **2** was found to be a versatile intermediate for palladium-catalysed coupling reactions, completing a synthetic strategy that should be generally useful for the synthesis of other highly substituted 2-pyridones.

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