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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. © 1999 Elsevier Science Ltd. All rights reserved.

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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 compounds³ 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.



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 5trifluoromethanesulfonyloxy-2-pyridones⁶ 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 reagent⁸ (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 conditions¹⁰ 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 chloride¹² to provide the desired acyl enamine 6 in good yield (59%) accompanied by small amounts ($\leq 10\%$) 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, H₂O, DMSO, 150°C (87%); iii) MeNH₂, TiCl₄, CHCl₃, 0°C; iv) CIOCCH₂OBn, THF, 0°C (59%, two steps); v) POCl₃, DMF, 0–75°C *then* H₂O, 0°C (48%); vi) Pd-C, HCO₂NH₄, AcOH, MeOH, rt (75%); vii) (CF₃SO₂)₂O, pyridine, CH₂Cl₂, -78–0°C (90%)

Scheme 1

Treatment of 6 with POCl₃-DMF at elevated temperature⁹ gave a 1-methyl-2-chloropyridinium

species¹³ 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.



Scheme 2

Fable 1							
No.	Method*	M–R	Yield ^b (%)	No.	Method*	M–R	Yield ^b (%)
1	A	(HO) ₂ B	61	12°	В	SEM. N CIZn N N Me	51
2 3 4 5	A	2-ON 3-ON 4-ON 4-O	1e 63 1e 70 1e 41 1 36	13°	В	SEM, N-N CIZn and isomer	28
6 7 8 9		(HO)₂B R 4-F 4-CI 3-NI 3-NI 3-N($ \begin{array}{c c} 47 \\ 47 \\ 21 \\ 4_2 \\ 61 \\ 0_2 \\ 29 \\ \end{array} $	14 ^d	С	Bu ₃ Sn O	44
10	A	(HO)2B	67	15	D	CO ₂ Me	41
11	А	(HO) ₂ B	69	16	E	ОН	27

^aMethod A: Pd(PPh₃)₄, Na₂CO₃, DME-H₂O, 100°C; Method B: Pd(PPh₃)₄, THF, 50°C; Method C: Pd(PPh₃)₄, DMF, 100°C; Method D: Pd(OAc)₂, PPh₃, LiCl, Et₃N, 100°C; Method E: Pd(PPh₃)₄, CuI, Et₃N, 100°C. ^bIsolated yields (unoptimised) of final compounds with purity of 95-99% as measured by hplc. ^cOrganozinc formed by deprotonation of a mixture of the regioisomeric protected heterocycle with Bu^aLi and transmetalation with ZnCl₂ (ref. 17). The major isomer is shown. ^dref. 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 conditions¹⁴ and these reactions were conveniently carried out in parallel in batches of 5-12 compounds.¹⁵

Other heterocycles were introduced by Negishi coupling¹⁶ of the organozinc halides¹⁷ (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 coupling¹⁸ of a heterocyclic stannane¹⁹ to the triflate **2** was also effective (entry 14) and the successful Heck²⁰ and Sonogashira²¹ 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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