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6-Trifluoromethanesulfonyloxy-4(3H)-pyrimidinones as Versatile Intermediates for the Synthesis of 6-Functionalized 4(3H)-Pyrimidinones

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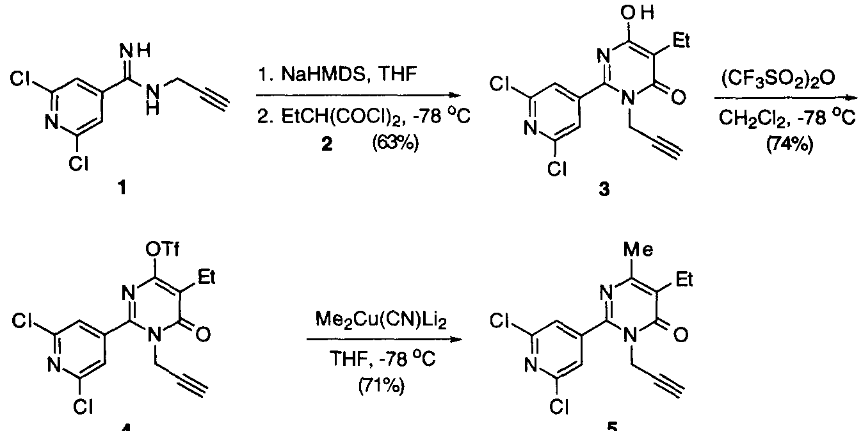
Summary: The reaction of 6-trifluoromethanesulfonyloxy-4(3H)-pyrimidinones with $Me_2Cu(CN)Li_2$, and with vinyl tributyltin, trimethylsilylacetylene, and zinc cyanide with palladium catalysis, are described for the synthesis of a variety of fully functionalized 6-substituted-4(3H)-pyrimidinones of interest as herbicides.

Pyrimidinones are of broad medicinal and agricultural interest,[1,2] and numerous methods have been developed for their preparation.[3] During a recent study of possible routes to the fully functionalized 4(3H)-pyrimidinone (**5**) as a promising new herbicide, we examined many of these traditional methods with very limited success. These difficulties certainly arise in part from the peculiar structural features of our target 4(3H)-pyrimidinones, since the 2,6-dichloropyridyl and propargyl substituents pose steric problems and are chemically reactive under many reaction conditions.[2] We describe in this paper a facile and flexible strategy for the preparation of 4(3H)-pyrimidinone **5** via the 6-trifluoromethanesulfonyloxy intermediate **4** (Scheme 1), as well as an extension of this methodology to the preparation of a number of related analogues.

Addition of propargylamine hydrochloride to 2,6-dichloro-4-cyanopyridine in the presence of a catalytic amount of sodium methoxide generated the carboxamidine hydrochloride **1**. Formation of the anion of this amidine with sodium bis(trimethylsilyl)amide (NaHMDS) at -78 °C followed by addition of 2-ethylmalonyl dichloride (**2**)[4,5] yielded 2-(2,6-dichloro-4-pyridyl)-5-ethyl-6-hydroxy-3-propargyl-4(3H)-pyrimidinone (**3**).[6] The choice of NaHMDS as a strong base was mandated by the necessity of carrying out anion formation under sufficiently mild conditions to avoid self-condensation of the free amidine which occurs at higher temperatures.[2]

There remained the challenge of converting the 6-hydroxy functionality in **3** to a methyl substituent. We initially considered both 6-methoxy and 6-mesyloxy groupings, followed by displacement with methyl anion equivalents, but none of the desired **5** was



1 3 4 5

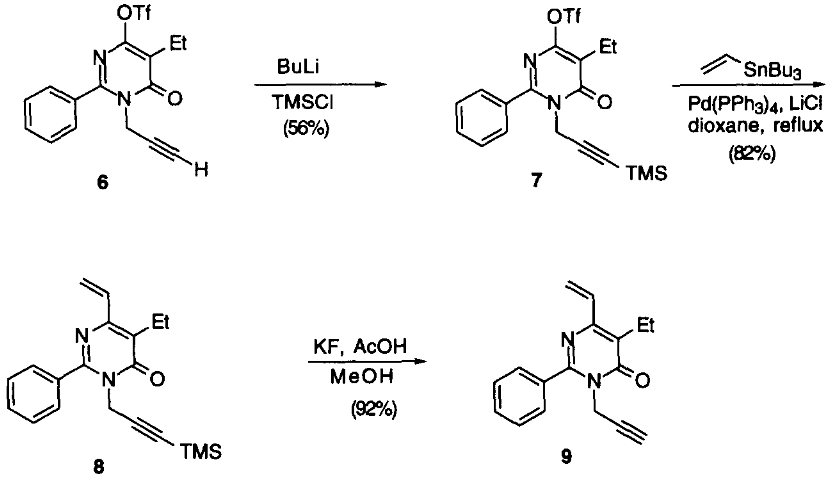
Scheme 1

observed in these reactions. We then turned to the 6-trifluoromethanesulfonyloxy (triflate) derivative **4**,[7] which was prepared in 74% yield by the reaction of **3** with triflic anhydride at -78 °C in methylene chloride, in the presence of collidine as base. Initial studies with methylmagnesium bromide/cuprous iodide, or with methyl lithium/cuprous iodide, also failed. However, treatment of **4** with $Me_2Cu(CN)Li_2$ in dry THF[8] resulted in a smooth reaction to provide the target 4(3H)-pyrimidinone **5** in 71% isolated yield. No protection of the 3-propargyl substituent was necessary.

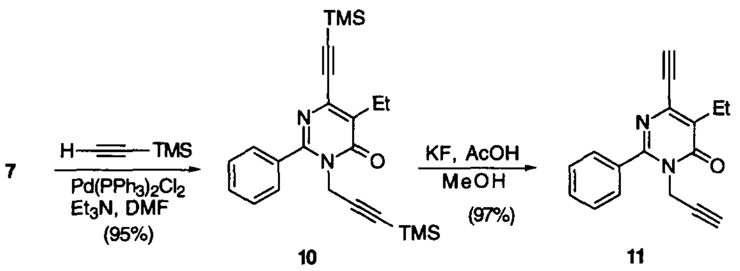
2-Phenyl-5-ethyl-6-trifluoromethanesulfonyloxy-3-propargyl-4(3H)-pyrimidinone (**6**) was prepared by a procedure analogous to that described above for the preparation of triflate **4**, and this new compound (protected as described below) proved to be a versatile intermediate for the preparation of a variety of 2-phenyl-6-substituted variants of compound **5**. Thus, the propargyl functionality in **6** was first protected by treatment with butyllithium followed by addition of trimethylsilyl chloride (Scheme 2). Stille coupling of the resulting 3-(3-trimethylsilyl)propargyl derivative **7**[9] with vinyl tributyltin in the presence of $Pd(PPh_3)_4$ and LiCl gave the 6-vinyl-4(3H)-pyrimidinone **8** (82% yield),[10] which was deprotected with potassium fluoride/acetic acid in methanol to give **9**[11] in 92% yield. With tetrabutylammonium fluoride and in the absence of an available proton source, yields of **9** were much lower.

In analogous fashion (Scheme 3), coupling of **7** with trimethylsilylacetylene in the presence of $Pd(PPh_3)_2Cl_2$ gave the 6-(trimethylsilylethynyl) derivative **10** in 95% yield.[12] Double desilylation, again with potassium fluoride/acetic acid in methanol, led to the 6-ethynyl-3-propargyl-4(3H)-pyrimidinone **11**[13] in 97% isolated yield.

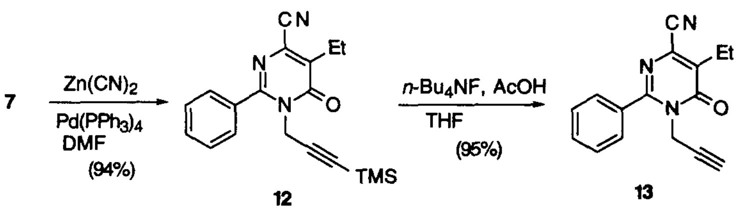
Finally (Scheme 4), the 6-cyano derivative **13**[14,15] was prepared in 89% overall yield (from **7**) by coupling of **7** with 98% zinc cyanide[16] in the presence of $Pd(PPh_3)_4$, followed by desilylation of the resulting **12** as described above.



Scheme 2



Scheme 3



Scheme 4

These demonstrations of the versatility of the triflates **4** and **7** towards addition/elimination and palladium-catalyzed C-C coupling reactions suggest that many additional derivatives of the above class of 4(3H)-pyrimidinone herbicides should be readily available.

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2. See the preceding paper: Taylor, E. C.; Zhou, P.; Tice, C. M.; Lidert, Z.; Roemmele, R. C. *Tetrahedron Lett.* this issue.
3. Brown, D. J.; Evans, R. F.; Cowden, W. B.; Fenn, M. D. *The Pyrimidines*, Taylor, E. C. Ed., John Wiley & Sons, New York, **1994**.
4. 2-Ethyl malonyl dichloride was prepared in 86% yield by reacting commercially available 2-ethyl malonic acid with thionyl chloride.
5. Malonyl dichloride has been used previously for the construction of pyrimidinone rings; see (a) Ziegler, E.; Argyrides, A.; Steiger, W. *Monatsh. Chem.* **1971**, *102*, 301. (b) Steiger, W.; Argyrides, A; Ziegler, E. *Org. Prep. Proc. Int.* **1972**, *4*, 253.
6. Compound **3** has the following physical and spectroscopic properties: mp 200-202 ^{o}C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.11 (t, J=7.6 Hz, 3H), 2.44-2.54 (m, 3H), 4.59 (d, J=2.3 Hz, 2H), 7.59 (s, 2H), 9.25 (br s, 1H).
7. Compound **4** has the following physical and spectroscopic properties: mp 112-114 ^{o}C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.24 (t, J=7.6 Hz, 3H), 2.56 (t, J=2.3 Hz, 1H), 2.66 (q, J= 7.6 Hz, 2H), 4.63 (d, J=2.3 Hz, 2H), 7.66 (s, 2H).
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9. Compound **7** has the following physical and spectroscopic properties: mp 119-120 ^{o}C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.20 (s, 9H) 1.23 (t, J=7.3 Hz, 3H), 2.64 (q, J=7.3 Hz, 2H), 4.66 (s, 2H), 7.50-7.80 (m, 5H).
10. For the reaction of aryl triflates with organostannanes, see ref. 8 (a).
11. Compound **9** has the following physical and spectroscopic properties: mp 113-115 ^{o}C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.01 (t, J=7.3 Hz, 3H), 2.16 (t, J=1.3 Hz, 1H), 2.37 (q, J=7.5 Hz, 2H), 4.41 (d, J=1.3 Hz, 2H), 5.44 (dd, J_1=2.0 Hz, J_2=10.5 Hz, 1H), 6.30 (dd, J_1=2.0 Hz, J_2=16.8 Hz, 1H), 6.73 (dd, J_1=10.5 Hz, J_2=16.8 Hz, 1H), 7.33-7.57 (m, 5H).
12. For the palladium-catalyzed reaction of aryl triflates with acetylenes, see (a) ref. 8(a). (b) Barbier, M. ; Devys, M.; Parisot, D. *Syn. Commun.* **1993**, *23*, 1481.
13. Compound **11** has the following physical and spectroscopic properties: mp 134-136 ^{o}C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.06 (t, J=7.3 Hz, 3H), 2.17 (t, J=2.3 Hz, 1H), 2.61 (q, J=7.3 Hz, 2H), 3.29 (s, 1H), 4.40 (d, J=2.3 Hz, 2H), 7.29-7.51 (m, 5H).
14. Compound **13** has the following physical and spectroscopic properties: mp 132-133 ^{o}C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.31 (t, J=7.3 Hz, 3H), 2.40 (t, J=2.3 Hz, 1H), 2.83 (q, J=7.3 Hz, 2H), 4.60 (d, J=2.2 Hz, 2H), 7.50-7.75 (m, 5H).
15. For the palladium-catalyzed reaction of aryl triflates with zinc cyanide, see; Selnick, H. G.; Smith, G. R.; Tebben, A. J. *Syn. Commun.* **1995**, *25*, 3255.
16. From Aldrich Chemical Company

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