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Synthesis of 2-(2,6-Dichloro-4-pyridyl)-3-propargyl-5-ethyl-6-methyl-4(3H)-pyrimidinone, a Promising New Herbicide

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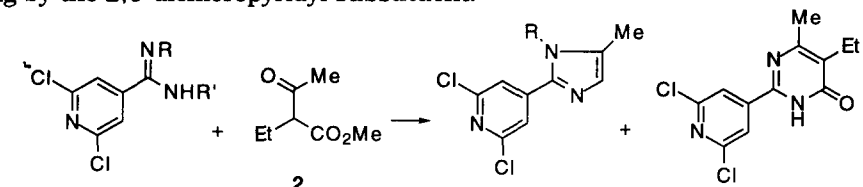
*Summary: A novel synthesis of the promising new herbicide 2-(2,6-dichloro-4-pyridyl)-3-propargyl-5-ethyl-6-methyl-4(3H)-pyrimidinone (**12**) is reported which features (1) regioselective carbon, followed by nitrogen, dialkylation of an intermediate dianion, and (2) a tandem "one-pot" sequence of reactions involving sigmatropic sulfoxide elimination, lithium chloride-induced demethylation of a carbomethoxy grouping, decarboxylation, and isomerization/aromatization.* © 1997 Elsevier Science Ltd.

The design and synthesis of new herbicides is a continuing challenge in agricultural chemistry because of the persistent problem of resistance development, and as a result of economic and environmental pressures to find compounds with different modes of action. We report herein a novel synthesis of a promising new herbicide, 2-(2,6-dichloro-4-pyridyl)-3-propargyl-5-ethyl-6-methyl-4(3H)-pyrimidinone (**12**).[1]

Many synthetic approaches are available for the construction of 4-pyrimidinones.[2] None of these proved in our hands to be effective for the synthesis of **12**. As an example, condensation of the N-propargyl amidine **1b** with the β-ketoester **2** led only to the imidazoles **3a** and **3b**, together with the N-unsubstituted 4-pyrimidinone **4**; none of the anticipated N-propargyl compound **12** was obtained. It appears that disproportionation of **1b** gave a mixture of the N,N'-dipropargyl amidine **1c** and the N-unsubstituted amidine **1a**; subsequent condensation of **1a** with **2** then gave **4**, while thermal cyclization and aromatization of **1b** and **1c** gave rise to the imidazoles **3a** and **3b** respectively.[3] Propargylation of **4** yielded only a trace of the target N-propargyl compound **12**; the

dominant product was the result of O-alkylation, apparently as a consequence of steric crowding by the 2,6-dichloropyridyl substituent.



1a, R = R '= H
b, R = H, R' = propargyl
c, R = R' = propargyl

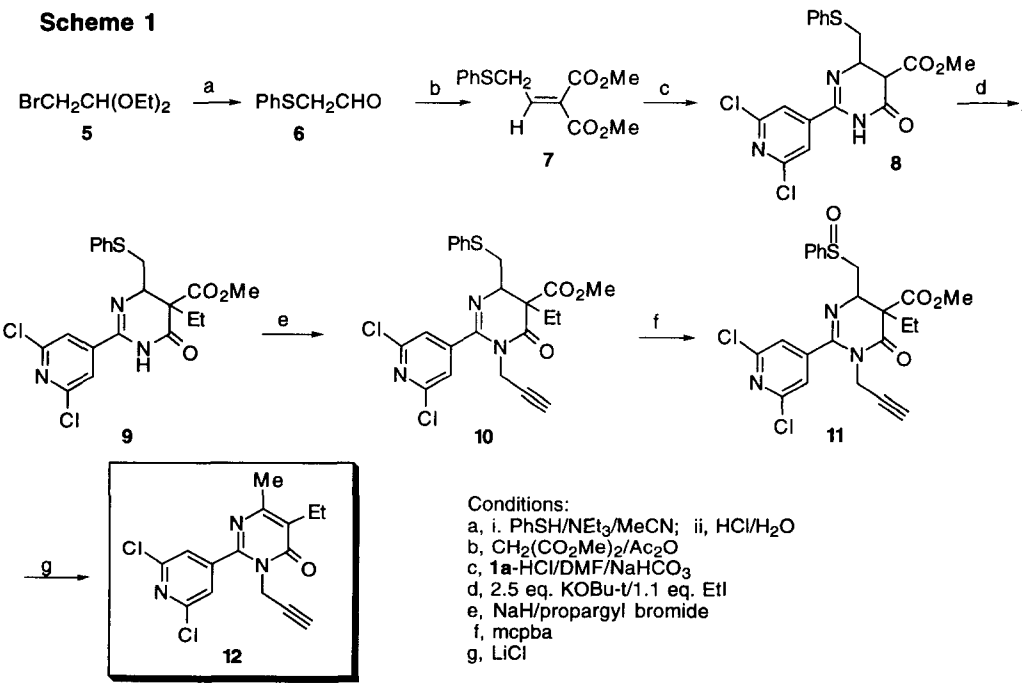
2

3a, R = H
b, R = propargyl

4

Target pyrimidinone **12** was finally prepared by the novel sequence of reactions outined in Scheme 1. Reaction of commercially available bromoacetaldehyde diethylacetal with thiophenol in the presence of triethylamine, followed by an aqueous workup, gave phenylthioacetaldehyde (**6**) in 64% yield. An aldol condensation of **6** with dimethyl malonate in the presence of acetic anhydride then gave dimethyl 2-phenthiomethylenemalonate (**7**). Condensation of this extremely active Michael acceptor with amidine **1a** then gave the dihydropyrimidinone **8** in 53-65% yield following either flash chromatography or trituration with hexane.[4]

Scheme 1



Conditions:
a, i. $PhSH/NEt_3/MeCN$; ii, HCl/H_2O
b, $CH_2(CO_2Me)_2/Ac_2O$
c, **1a**-$HCl/DMF/NaHCO_3$
d, 2.5 eq. KOBu-t/1.1 eq. EtI
e, NaH/propargyl bromide
f, mcpba
g, LiCl

Regioselective alkylation of dianions to effect substitution at the less acidic position is a widely utilized, generally effective methodology,[5] and this protocol was successfully applied to compound **8**. Thus, treatment of **8** with 2.5 equivalents of potassium tert-butoxide in DMF smoothly generated a dianion which was quenched with 1.1 equivalents of ethyl iodide to give the 5-ethyl derivative **9** in 91% isolated yield.[6] No competing N-alkylation was observed under these conditions. Subsequent treatment of **9** with sodium hydride followed by addition of propargyl bromide then produced the N-propargyl compound **10** in 85% yield.[7] In this second alkylation, it was gratifying to observe that no O-propargylation occurred, apparently as a consequence of severe steric congestion arising from the flanking quaternary carbon at C-5.

Oxidation of the sulfide **10** with m-chloroperbenzoic acid gave the sulfoxide **11** (99%) which was then converted *in a single step* to **12** by heating with lithium chloride in refluxing pyridine (24%). This one-pot transformation involves sigmatropic sulfoxide elimination,[8] lithium chloride-induced demethylation of the carbomethoxy grouping at C-5,[9] decarboxylation, and final isomerization/aromatization.[10]

A full report on the herbicidal activity of 2-(2,6-dichloro-4-pyridyl)-3-propargyl-5-ethyl-6-methyl-4(3H)-pyrimidinone (**12**) will be published separately.

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2. Brown, D. J.; Evans, R. F.; Cowden, W. B.; Fenn, M. D. *The Pyrimidines, Supplement II*, Taylor, E. C. Ed., John Wiley & Sons, New York; 1994.
3. (a) *The Chemistry of Functional Groups: The Chemistry of Amidines and Imidates*, Patai, S., Ed: John Wiley & Sons, New York; 1975. (b) Similar cyclization reactions have been reported for the preparation of oxazoles, thiazoles and imidazoles. See Eloy, F.; Deryckere, A. *Chim. Ther.* **1973**, *8*, 437. *Chem. Abstr.* **1974**, *81*, 13439; Overman, L. E.; Roos, J. P. *J. Org. Chem.* **1981**, *46*, 811. (c) These results require the intermediacy of the N,N'-dipropargyl amidine **1c** and the N-unsubstituted amidine **1a**, which presumably arise from amidine exchange reactions involving ammonia and propargylamine (from decomposition and/or hydrolysis of **1b**). Subsequent condensation of **1a** with **2** would give **4**, while thermal cyclization and aromatization of **1b** and **1c** would give rise to the imidazoles **3a** and **3b** respectively.

4. Compound **8** has the following physical and spectroscopic properties: mp 155-6 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.21 (dd, J_1=5.3 Hz, J_2=14.2 Hz, 1H), 3.41 (dd, J_1=5.6 Hz, J_2=14.3 Hz, 1H), 3.77 (s, 3H), 3.89 (d, J=9.9 Hz, 1H), 4.45-4.55 (m, 1H), 7.22-7.45 (m, 5H), 7.53 (s, 2H), 9.27 (br s, 1H).

5. For an excellent review on dianion chemistry, see Thompson, C. M.; Green, D. L. C. *Tetrahedron* **1991**, *47*, 4223.

6. Compound **9** has the following physical and spectroscopic properties: mp 175-7°C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.86 (t, J=7.3 Hz, 3H), 1.90-2.05 (m, 1H), 2.30-2.46 (m, 1H), 3.34-3.67 (m, 2H), 3.68 (s, 3H), 3.91-3.96 (m, 1H), 7.25-7.49 (m, 5H), 7.65 (s, 2H), 9.79 (br s, 1H).

7. Compound **10** has the following physical and spectroscopic properties: mp 129-130 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.87 (t, J=7.3 Hz, 3H), 1.90-2.08 (m, 1H), 2.32-2.45 (m, 2H), 3.38-3.40 (m, 2H), 3.74 (s, 3H), 3.84 (t, J=7.3 Hz, 1H), 4.25 (dd, J_1=2.2 Hz, J_2=17.6 Hz, 1H), 4.37 (dd, J_1=2.2 Hz, J_2=17.6 Hz, 1H), 7.29-7.51 (m, 7H).

8. For a discussion of sigmatropic sulfoxide elimination, see (a) Trost, B. M.; Parquette, J. R. *J. Org. Chem.* **1993**, *58*, 1579. (b) Ohta, A.; Tonomura, Y.; Odashima, H.; Fujiwara, N.; Shimazaki, M. *Heterocycles*, **1989** *29*, 1199.

9. For lithium halide-mediated decarboxylation of carboxylic esters, see (a) Cherbuliez, E.; Leber, J.-P.; Bouvier, M. *Helv. Chim. Acta* **1953**, *36*, 1203. (b) Elsinger, F. *Org. Syn.* **1964**, *45*, 7. (c) McMurry, J. E.; Wong, G. B. *Syn. Commun.* **1972**, *2*, 389.

10. Compound **12** has the following physical and spectroscopic properties: mp 143-144 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.16 (t, J=7.6 Hz, 3H), 2.35 (s, 3H), 2.43 (t, J=2.6 Hz, 1H), 2.62 (q, J=7.6 Hz, 2H), 4.56 (d, J=2.6 Hz, 2H), 7.60 (s, 2H).

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