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Shridhar G. Hegde [a] & Robert D. Bryant [a]
[a] New Products Division , The Agricultural Group of Monsanto , A Unit of Monsanto Company, St. Louis, Missouri, 63167
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ANNULATION WITH METHYL 4-(TRIPHENYLPHOSPHORANYLIDENE)ACETOACETATE. APPLICATION TO THE SYNTHESIS OF A 1,3-BENZENEDICARBOXYLATE DERIVATIVE

Shridhar G. Hegde* and Robert D. Bryant

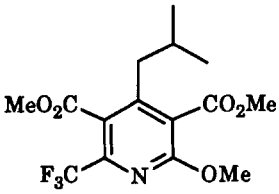
New Products Division, The Agricultural Group of Monsanto,
A Unit of Monsanto Company, St. Louis, Missouri 63167

Abstract: A synthesis of cyclohexenone **3** via an annulation reaction of 4-(triphenylphosphoranylidene)acetoacetate and aromatization of **3** to a 1,3-benzenedicarboxylate derivative are described.

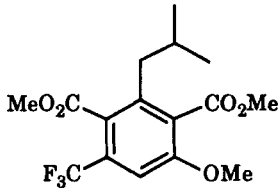
The herbicidal properties of 2,6-(polyfluoroalkyl)-3,5-pyridinedicarboxylates were first described by Lee et al in 1985.[1] Since then a large number of analogous pyridine derivatives have been reported as herbicides.[2] Recently, the 2-methoxy-6-(trifluoromethyl)pyridine derivative **1** was shown to be a highly active member of this series.[3] As part of a structure-activity correlation study of the pyridine herbicides, we needed to prepare the 1,3-benzenedicarboxylate **2** as an

* To whom correspondence should be addressed.

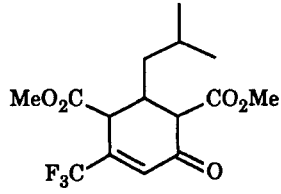
analog of compound **1** in order to determine the importance of ring nitrogen atom for activity.



1



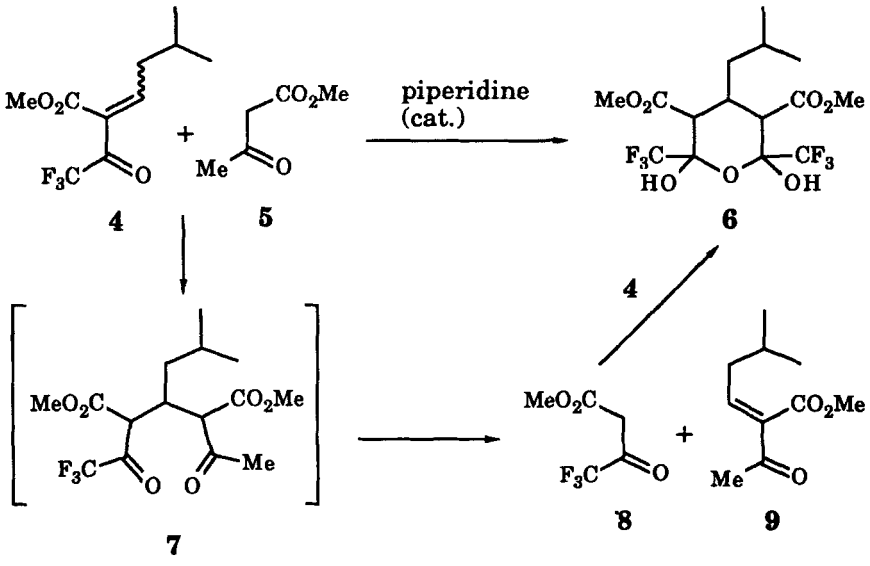
2



3

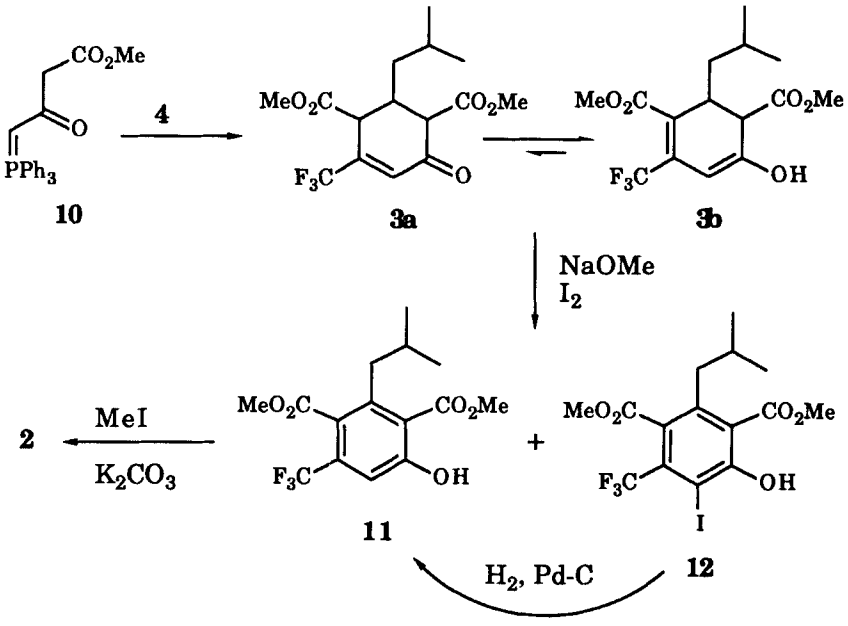
We envisioned the synthesis of **2** from a cyclohexenone precursor **3** via aromatization to the corresponding phenol and methylation. Initially we had expected to prepare compound **3** from an annulation reaction of methyl acetoacetate (**5**) and methyl 5-methyl-2-(trifluoroacetyl)-2-hexenoate (**4**)[4], the condensation product of methyl trifluoroacetoacetate and isovaleraldehyde. However, treatment of a mixture of **4** and **5** in THF with a catalytic amount of piperidine at room temperature gave the pyran derivative **6** (~ 45%) as the major product as determined by GC-mass spectrometry and ^{1}H nmr (scheme I). In addition, methyl 2-acetyl-5-methyl-2-hexenoate (**9**) and unreacted **5** were also detected in the product mixture. The mechanism of formation of pyran **6** most likely involves a cleavage of the initial michael adduct **7** to methyl trifluoroacetoacetate (**8**) and the alkylidene derivative **9**, and subsequent condensation of **8** with unreacted **4**. Indeed, pyran **6** can also be prepared by base-catalyzed condensation of isovaleraldehyde with two equivalents of methyl trifluoroacetoacetate (**8**) as reported previously.[5]

Scheme I



Herein we report that a solution to the problem was achieved by replacing methyl acetoacetate (**5**) by its 4-(triphenylphosphoranylidene) derivative **10**[6,7] in the condensation with **4** (scheme II). Thus, mixing equimolar amounts of **10** and **4** in benzene or THF resulted in a mildly exothermic reaction and the desired cyclohexenone was produced in 76% yield as a mixture of enone and dienol tautomers **3a** and **3b** in 1:4 ratio.[8] We presume that the initial michael adduct, in this case, cyclizes sufficiently rapidly to overcome the propensity for cleavage to methyl trifluoroacetoacetate (**8**). Aromatization of the cyclohexenone was accomplished by an iodination-dehydroiodination sequence using iodine and sodium methoxide. Complete conversion of the starting material to aromatic products required 1.5 equivalents of iodine and 3.5 equivalents of sodium methoxide and the resulting

Scheme II



product mixture consisted of phenols **11** and **12** in approximately 1:1 ratio. This result can be explained by assuming a competitive mono- and diiodination of the enone. Dehydroiodination of the mono- and diiodinated intermediates gives phenols **11** and **12**, respectively. The crude mixture of **11** and **12** was then hydrogenated until all of **12** was converted to **11**. The overall yield of **11** from the mixture of **3a** and **3b** was 73%. Finally, phenol **11** was O-methylated with methyl iodide using potassium carbonate as the base to obtain the desired 1,3-benzenedicarboxylate **2** in 88% yield.

In summary, we have shown that the phosphoranylidine derivative **10** can be a useful alternative to methyl acetoacetate as an annulation reagent. In addition, we have provided a short and high yield synthesis of the 1,3-benzenedicarboxylate herbicide **2**.[9]

Experimental

All ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AM 360 NMR spectrometer at 360, 90 and 340 MHz, respectively, using $CDCl_3$ as the solvent. ^1H and ^{13}C chemical shifts (δ) are given in ppm relative to tetramethylsilane as the internal standard. ^{19}F chemical shifts (δ) are expressed in ppm relative to fluorotrichloromethane, with upfield shifts taken as negative. Preparative HPLC was performed on a Waters Prep 500 system with a 25 mm steel column packed with Kieselgel 60 (230-400 mesh). Compounds **4**[4] and **10**[6] were prepared according to the published procedures.

Dimethyl 2-(2-methylpropyl)-6-oxo-4-(trifluoromethyl)-4-cyclohexene-1,3-dicarboxylate (3a) and Dimethyl 6-hydroxy-2-(2-methylpropyl)-4-(trifluoromethyl)-3,5-cyclohexadiene-1,3-dicarboxylate (3b). To a solution of 10.0 g (0.042 mol) of **4** in 100 mL of benzene was added 15.8 g (0.042 mol) of **10** in small portions. A mildly exothermic reaction was accompanied by the dissolution of solids. After stirring at room temperature for 4 h, the solution was evaporated and the residue was purified by Kugelrohr distillation (oven temp. 105 °C, 1 mm Hg) to obtain 10.7 g (76%) of a 1:4 mixture of **3a** and **3b**: ^1H NMR δ 0.80-1.1 (m, 6H), 1.13-1.56 (m, 3H), 3.23-3.26 (m, 1H), 3.28 (s, 1H), 3.70 (s, 3H), 3.73 (s, 3H), 6.54 (m, 0.2H, =CH of **3a**), 6.60 (m, 0.8H, =CH of **3b**), 11.7 (s, 0.8H, =C-OH of **3b**); ^{13}C NMR **3a**: δ 22.1, 22.7, 26.3, 39.7, 43.2, 48.0, 53.0, 53.4, 121.8 (q, J = 270 Hz), 127.4, 145.5 (q, J = 32.4 Hz), 168.9, 170.6, 193.3 (C=O), **3b**: δ 21.2, 23.4, 25.1, 33.7, 41.2, 52.0, 52.8, 101.8, 122.6 (q, J = 270 Hz), 127.1, 131.2 (q, J = 32.4 Hz), 162.1 (=C-OH),

170.9, 171.7; ^{19}F NMR **3a**: δ - 68.8, **3b**: δ - 70.9. Anal. calcd. for $C_{15}H_{19}F_3O_5$: C, 53.57; H, 5.69. Found: C, 53.57; H, 5.73.

Dimethyl 4-hydroxy-2-(2-methylpropyl)-6-(trifluoromethyl)-1,3-benzenedicarboxylate (11). To a solution of 6.05 g (0.018 mol) of **3** in 100 mL of methanol was added to 3.9 g (0.072 mol) of sodium methoxide in 15 mL of methanol. The resulting yellow solution was cooled to 0 °C and 6.9 g (0.027 mol) of iodine was added in small portions over a period of 1 h. The solution was then warmed to room temperature and stirred for an additional 3 h. The excess of iodine was destroyed by adding saturated aqueous sodium thiosulfate and the solution was evaporated. The residue was acidified with 10% HCl (100 mL) and extracted with ether (3 x 100 mL). The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated. Analysis of the residue by gc-mass spectrometry and ^1H NMR indicated compounds **11** and **12** in approximately 1:1 ratio.

A mixture of the crude product in 50 mL of methanol and 0.4 g of 10% palladium on carbon was shaken under a hydrogen atmosphere (3 atm) for 24 h. After removing the catalyst by filtration, the solution was evaporated and the residue was purified by preparative HPLC (5% EtOAC/hexane) to obtain 4.4 g (73%) of compound **11** as a colorless oil: ^1H NMR δ 0.80 (d, 6H, J = 7.2 Hz), 1.72 (m, 1H), 2.47 (d, 2H, J = 7.2 Hz), 3.76 (s, 3H), 3.85 (s, 3H), 7.02 (s, 1H); ^{13}C NMR δ 21.5, 28.7, 36.6, 52.1, 56.4, 108.4, 121.5 (q, J = 270 Hz), 122.7, 126.2, 128.5 (q, J = 34 Hz), 138.7, 152.3, 166.8, 168.2; ^{19}F NMR δ - 64.6. Anal. calcd. for $C_{15}H_{17}F_3O_5$: C, 53.89; H, 5.13. Found: C, 53.72; H, 5.04.

Dimethyl 4-methoxy-2-(2-methylpropyl)-6-(trifluoromethyl)-1,3-benzenedicarboxylate (2). A solution of 3.34 g (0.01 mol) of **11** and 2.13 g (0.015 mol) of methyl iodide in 100 mL of acetone was added to 2.76 g (0.02 mol) of anhydrous potassium carbonate and the resulting suspension was heated at reflux for 16 h. The reaction mixture was filtered to remove insoluble salts and the filtrate was evaporated. The residue was diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water, dried ($MgSO_4$), and evaporated. Kugelrohr distillation (oven temp. 120 °C, 1 mm Hg) of the residue gave 3.05 g (88%) of compound **2** as a colorless oil: ^1H NMR δ 0.85 (d, 6H, J = 7.2 Hz), 1.78 (m, 1H), 2.55 (d, 2H, J = 7.2 Hz), 3.85 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 7.05 (s, 1H); ^{13}C NMR δ 22.3, 29.4, 39.5, 52.3, 52.4, 56.0, 106.5, 123.0 (q, J = 270 Hz), 125.1, 127.8, 129.7 (q, J = 31.5 Hz), 139.5, 156.6, 167.0, 167.5; ^{19}F NMR δ - 62.3. Anal. calcd. for $C_{16}H_{19}F_3O_5$: C, 55.17; H, 5.50. Found: C, 55.16; H, 5.47.

References and Notes

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7. For examples of annulation reaction of compound **10** with α,β-unsaturated aldehydes, see: (a) Pietrusiewicz, K. M.; Monkiewicz, J.; Bodalski, R., J. Org. Chem., 1983, 48, 788. (b) Moorhoff, C. M. and Schneider, D. F., Tetrahedron Lett., 1987, 28, 4721. (c) Pietrusiewicz, K. M. and Salamonczyk, I., J. Org. Chem., 1988, 53, 2837.

8. The ^{1}H, ^{13}C and ^{19}F nmr of the mixture of **3a** and **3b** indicated a single stereoisomer of each compound. The relative stereochemistry of the isobutyl and the methoxycarbonyl groups in **3b** was tentatively assigned to be *trans* based upon the fact that the cyclohexyl ring proton adjacent to the methoxycarbonyl group displayed a sharp singlet at 3.28 ppm in the ^{1}H nmr spectrum. The lack of coupling with the adjacent ring proton is consistent with a dihedral angle of approximately 90^{0} as deduced from a molecular model of the *trans* isomer. The stereochemistry of **3a** could not be assigned unambiguously.

9. Compound **2** was approximately ten-fold less active than **1** as a herbicide. A detailed comparison of biological activities will be published separately.

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