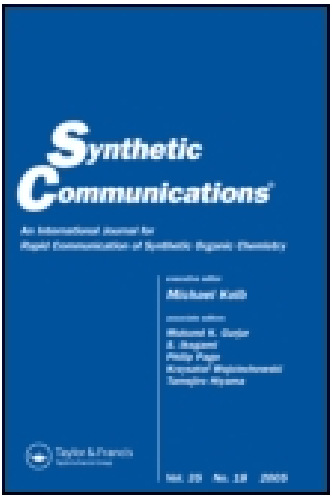


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A REGIOSPECIFIC SYNTHESIS OF 3,3,6-TRIMETHYLINDAN-1-ONE

Paul F. Vogt [a] , Bruce F. Molino [a] & Albert J. Robichaud [b]

[a] Department of Medicinal Chemistry , Albany Molecular Research, Inc. , 21 Corporate Circle, Albany, NY, 12203, U.S.A.

[b] The DuPont Pharmaceuticals Company , Chemical & Physical Sciences, Experimental Station, Wilmington, DE, 19880, U.S.A.

Published online: 16 Aug 2006.

To cite this article: Paul F. Vogt , Bruce F. Molino & Albert J. Robichaud (2001) A REGIOSPECIFIC SYNTHESIS OF 3,3,6-TRIMETHYLINDAN-1-ONE, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:5, 679-684, DOI: 10.1081/SCC-100103256

To link to this article: http://dx.doi.org/10.1081/SCC-100103256

SYNTHETIC COMMUNICATIONS, 31(5), 679–684 (2001)

A REGIOSPECIFIC SYNTHESIS OF 3,3,6-TRIMETHYLINDAN-1-ONE

Paul F. Vogt,[1,*] Bruce F. Molino,[1] and Albert J. Robichaud[2]

[1]Department of Medicinal Chemistry, Albany Molecular Research, Inc., 21 Corporate Circle, Albany, NY 12203
[2]The DuPont Pharmaceuticals Company, Chemical & Physical Sciences, Experimental Station, Wilmington, DE 19880

ABSTRACT

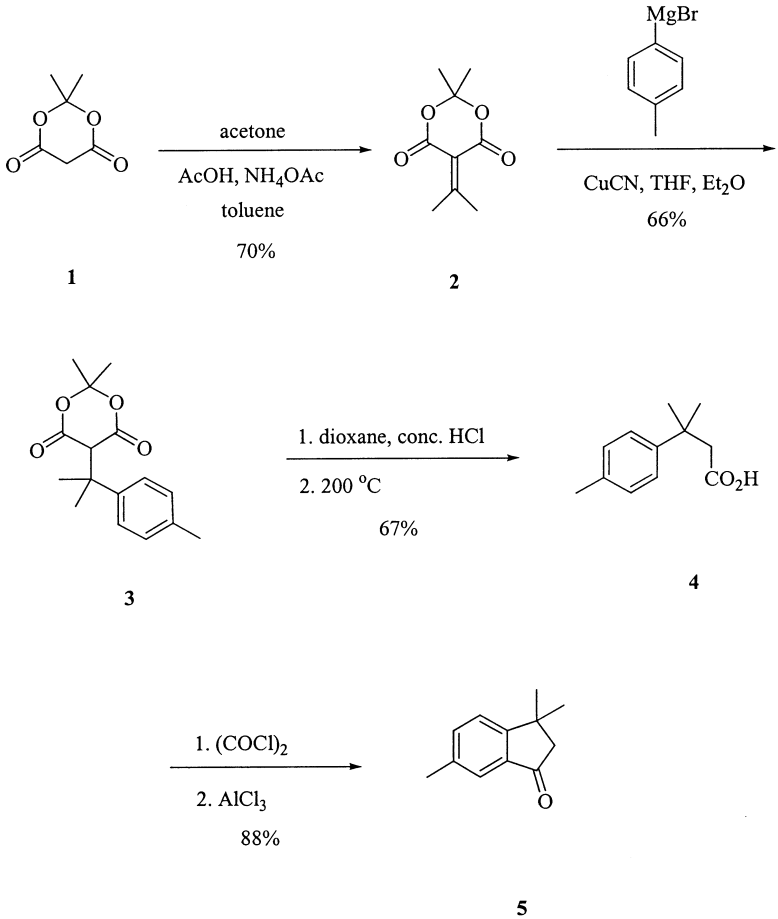
A novel, regiospecific synthesis of 3,3,6-trimethylindan-1-one (**5**) was achieved. The route to **5** was 6 steps and proceeded in 27% overall yield.

6-Substituted-3,3-dimethylindan-1-ones are key intermediates in the syntheses of several biologically relevant molecules[1] and in the course of a current research project we needed to prepare multi-gram quantities of 3,3,6-trimethylindan-1-one (**5**). Indanone **5** is a known compound and its synthesis from acid **4** has been reported.[2] To our knowledge, however, only one regiospecific route to acid **4**, and thus to indanone **5**, has appeared in the literature prior to this discovery.[3] This previous synthesis, which began with 4′-methylacetophenone, was 6 steps and produced **5** in 5–10% overall yield.[4]

We envisioned that a more efficient, regiospecific route to **4**, and thus to indanone **5**, could be developed. We are pleased to report that a regiospecific

* Corresponding author.

synthetic route to indanone **5** has been devised and is shown in Scheme 1. Thus, Meldrum's acid **(1)**[5] was condensed with acetone to give isopropylidene malonate **2** in 70% yield.[6] Michael addition of the cuprate generated from copper (I) cyanide and *p*-tolylmagnesium bromide, to isopropylidene malonate **2** gave Michael adduct **3** in 66% yield.[7] Michael adduct **3** was then hydrolyzed with concentrated HCl in dioxane, followed by thermal decarboxylation at 200°C to provide **4** in 67% yield.[8] 3-Methyl-3-*p*-tolyl butyric acid (**4**) was treated with oxalyl chloride and then cyclized to indanone **5** with aluminum chloride in one pot. The 3,3,6-trimethylindan-1-one **5** was isolated from the crude reaction mixture in 88% yield after bulb-to-bulb distillation.



Scheme 1.

The new synthetic route presented in this report provides a means to prepare multigram quantities of this important synthetic intermediate regiospecifically and in higher overall yield (27%) than methods previously reported. The number of chemical steps involved in this synthetic route is identical with previously reported syntheses.[4] However, the overall efficiency, as measured by ease of isolation and purification of intermediates and final product is vastly improved. Also, while the final cyclization of carboxylic acid **4** to indanone **5** is formally two distinct chemical steps, the reactions are conducted in one pot. One final comment regarding this novel route is that in principal, the regiospecific synthesis of other 6-substituted 3,3-dimethylindan-1-ones may be possible by introducing different para-substituted aryl grignards at the cuprate conjugate addition step.

EXPERIMENTAL

General

Proton NMR spectra were obtained on a Bruker AC 300 spectrometer at 300 MHz and were referenced to tetramethylsilane as an internal standard. Carbon NMR spectra were obtained on a Bruker AC 300 spectrometer at 75 MHz and were referenced to $CDCl_3$. The IR spectrometer used was a single beam Perkin-Elmer Spectrum 1000 FT-IR. All IR spectra obtained were prepared in a pressed disc of KBr. All IR spectra obtained were acquired with a total of 4 accumulations at a resolution of 4.00 cm^{-1}. Melting points were obtained on a Mel-Temp II apparatus and are uncorrected. CI Mass spectra were obtained on a Shimadzu QP-5000 Mass Spectrometer. FAB Mass spectra were obtained by M-Scan, Inc. of West Chester, PA.

5-Isopropylidiene-2,2-dimethyl-(1,3)-dioxane-4,6-dione (2)

To anhydrous toluene (250 ml) was added acetic acid (5.0 ml, 0.09 mol), ammonium acetate (1.4 g, 0.02 mol), acetone (25 ml, 0.34 mol), Meldrum's acid (49.7 g, 0.34 mol) and powdered 4 Å molecular sieves (ca. 50 g). After a stirring period of 6 h under nitrogen, an additional 25 ml of acetone was added. The mixture was stirred for an additional 18 h under nitrogen. The mixture was filtered to remove the molecular sieves and the filtrate was reduced to 1/3 its original volume. The resulting slurry was partitioned between toluene and sat. $NaHCO_3$. The organic layer

was washed with $NaHCO_3$ (2×), brine (1×), dried over $MgSO_4$, filtered and concentrated to yield a yellow solid. This solid was triturated with hexanes, filtered, and dried to yield a white solid (44.6 g, 70%): mp 68–71°C (lit.[6a] mp 73–78.5°C); IR 1751, 1719, 1286 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73 (s, 6H), 2.52 (s, 6H); ^{13}C NMR ($CDCl_3$) 26.4, 26.8, 103.1, 116.4, 160.8, 176.9 ppm; FAB MS m/z $[M+H]^+ = 185$.

5-(2-*p*-Tolylpropane)-(2,2)-dimethyl-(1,3)-dioxane-4,6-dione (3)

Copper (I) cyanide (60.8 g, 0.68 mol) was suspended in anhydrous THF and cooled in an ice/water bath with vigorous stirring. To the cold suspension was added dropwise, *p*-tolylmagnesium bromide (1.4 l of a 1.0 M etheral solution, 1.4 mol) over 1 h. The ice bath was removed and the reaction stirred at room temperature for 1 h. The mixture was cooled again in an ice/water bath and charged with a solution of **2** (59.6 g, 0.32 mol) in THF (250 ml) portionwise over 15 min. The ice bath was removed and the reaction mixture was stirred at room temperature for 16 h. The mixture was then quenched by addition of saturated aqueous NH_4Cl. The organic layer was separated and the aqueous layer was extracted with ether (3×). The combined ether layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give a yellow solid. This yellow solid was triturated with hexanes, filtered, and dried to give an off-white solid (59.1 g, 66%): mp 98–101°C; IR 1791, 1749, 1316 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (s, 3H), 1.62 (s, 3H), 1.65 (s, 3H), 2.31 (s, 3H), 3.57 (s, 1H), 7.13 (*d*, $J = 6.0$ Hz, 2H), 7.23 (*d*, $J = 9.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$) 20.8, 27.3, 27.8, 29.2, 42.3, 57.6, 105.0, 126.0, 128.9, 136.5, 141.6, 164.2 ppm; FAB MS m/z $[C_{10}H_{13}] = 133$.

3-Methyl-3-*p*-tolyl-butyric acid (4)

Michael adduct **3** (21.9 g, 0.08 mol) was dissolved in dioxane (125 ml) and concentrated HCl (50 ml) and was refluxed for 18 h. The reaction mixture was cooled to room temperature and concentrated. The resulting slurry was partitioned between water and methylene chloride. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The resulting brown solid was heated to 200°C in an oil bath for 1 h. The mixture was cooled to room temperature and the resulting solids were recrystallized from petroleum ether to yield a light brown solid (10.2 g, 67%): mp 76–78°C (lit.[2c] mp 77°C); IR 2978, 1698, 1315 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 6H), 2.32 (s, 3H), 2.63 (s, 2H), 7.12

(*d*, $J = 9.0$ Hz, 2H), 7.25 (d, $J = 6.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$) 20.8, 28.8, 37.1, 48.0, 67.0, 125.3, 128.9, 136.2, 145.9, 177.8 ppm; FAB MS m/z $[C_{10}H_{13}] = 133$.

3,3,6-Trimethylindan-1-one (5)

Acid **4** (29.8 g, 0.16 mol) was dissolved in 2,2-dichloroethane (250 ml) and DMF (0.5 ml). The reaction mixture was cooled in an ice/water bath and charged with oxalyl chloride (19.0 ml, 0.22 mol). The reaction mixture stirred at room temperature, under N_2, for 24 h. The reaction mixture was concentrated and the resulting brown oil was dissolved in 2,2-dichloroethane (250 ml) and cooled in an ice/water bath. To the cooled solution was added aluminum chloride (26 g, 0.20 mol) and the reaction mixture stirred for 14 h at room temperature. The reaction mixture was poured into ice water and stirred for 2 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated. The resulting brown oil was purified by bulb-to-bulb distillation (100–110°C, 0.1 mm Hg) to give a white solid (22.9 g, 88%): mp 35°C (lit.[2a] mp 42–43°C); IR 2953, 1699, 1283 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 6H), 2.39 (s, 3H), 2.58 (s, 2H), 7.49–7.37 (m, 2H), 7.51 (s, 1H); ^{13}C NMR ($CDCl_3$) 20.8, 29.8, 37.9, 53.1, 123.0, 135.2, 135.9, 137.1, 161.1, 205.5 ppm; CIMS m/z $[M+H]^+ = 175$.

REFERENCES

1. (a) Buckle, D.R.; Arch, J.R.S.; Edge, C.; Foster, K.A.; Houge-Frydrych, C.S.V.; Pinto, I.L.; Smith, D.G.; Taylor, J.F.; Taylor, S.G.; Tedder, J.M.; Webster, R.A.B. *J. Med. Chem.* **1991**, *34*, 919. (b) Atwal, K.S.; Ferrara, F.N.; Ding, C.Z.; Grover, G.J.; Sleph, P.G.; Dzwonczyk, S.; Baird, A.J.; Normandin, D.E. *J. Med. Chem.* **1996**, *39*, 304. (c) Bös, M.; Jenek, F.; Martin, J.R.; Moreau, J.-L.; Sleight, A.J.; Wichmann, J.; Widmer, U. *J. Med. Chem.* **1997**, *40*, 2762.
2. (a) Buechi, G.; Biemann, K.; Vittimberga, B.; Stool, M. *J. Amer. Chem. Soc.* **1956**, *78*, 2622. (b) Ferrero, C.; Helg, R. *Helv. Chim. Acta* **1959**, *6*, 2111. (c) Khalat, A.A. Roberts, R.M. *J. Org. Chem.* **1971**, *36*, 1040. (d) Cologne, J.; Weinstein, G. *Bull. Soc. Chin. Fr.* **1951**, 961.
3. (a) Smith, J.G.; Massicotte, M.P. *Org. Prep. Proc. Int.* **1978**, *10*, 123. (b) Ruchardt, C. *Chem. Ber.* **1961**, 2609. (c) Khalaf, A.A. *Indian. J. Chem.*

1974, *12*, 476. (d) Brouwer, D.M.; van Doom, J.A.; Kiffen, A.A.; Kramer, P.A. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 189.
4. (a) Colonge, J.; Pichat, L. *Bull. Soc. Chim. Fr.* **1949**, 177. (b) Hukki, J. *Acta. Chem. Scand.* **1949**, *3*, 279.
5. (a) Meldrum, N.A. *J. Chem. Soc.* **1908**, *93*, 598. (b) Davidson, D.; Bernhard, S.A. *J. Amer. Chem. Soc.* **1948**, *70*, 3426. (c) McNab, H. *Chem. Soc. Rev.* **1978**, 345.
6. (a) Hedge, J.A.; Kruse, C.W.; Snyder, H.R. *J. Org. Chem.* **1961**, *26*, 3166. (b) Huang, X.; Xie, L. *Synth. Commun.* **1986**, *16*, 1701.
7. (a) Huang, X.; Chan, C.-C.; Wu, Q.-L. *Tetrahedron Lett.* **1982**, *23*, 75. (b) Davis, A.P.; Egan, T.J.; Orchard, M.G.; Cunningham, D.; McArdle, P. *Tetrahedron* **1992**, *48*, 8725. (c) Huang, X.; Chan, C.C.; Wu, Q.L. *Synth. React. Inorg. Met.-Org. Chem.* **1982**, *12*, 549.
8. Sato, M.; Kano, K.; Kitazawa, N. *Heterocycles* **1990***, 31, 1229.*

Received in the U.S.A. June 10, 2000