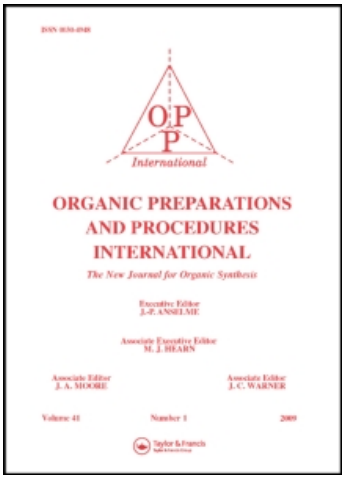

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN IMPROVED SYNTHESIS OF 1,3-BIS(5-*t*-BUTYL-2-SUBSTITUTED PHENYL)PROPANES

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To cite this Article Yamato, Takehiko , Tsuge, Akihiko , Koya, Keizo , Kobayashi, Kazumasa , Sakamoto, Hiroshi and Tashiro, Masashi(1987) 'AN IMPROVED SYNTHESIS OF 1,3-BIS(5-*t*-BUTYL-2-SUBSTITUTED PHENYL)PROPANES', Organic Preparations and Procedures International, 19: 1, 39 — 44
To link to this Article: DOI: 10.1080/00304948709354868
URL: http://dx.doi.org/10.1080/00304948709354868

ORGANIC PREPARATIONS AND PROCEDURES INT. 19(1), 39-82 (1987)

OPPI BRIEFS

AN IMPROVED SYNTHESIS OF 1,3-BIS(5-t-BUTYL-2-SUBSTITUTED PHENYL)PROPANES

Submitted by (08/27/85) Takehiko Yamato, Akihiko Tsuge, Keizo Koya, Kazumasa Kobayashi, Hiroshi Sakamoto, and Masashi Tashiro*

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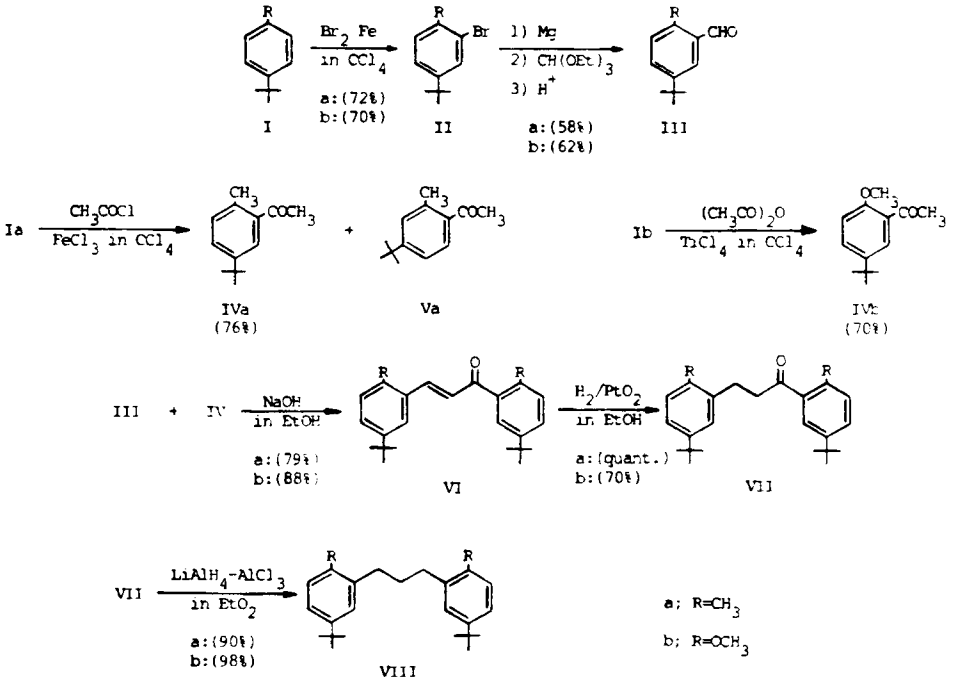
A shorter and more convenient route (Scheme 1) for the preparation of 1,3-bis(5-t-butyl-2-substituted phenyl)propanes in six steps has been devised starting from t-butyltoluene. The acetylation of Ia with acetyl chloride in the presence of $FeCl_3$ afforded mainly IVa while the same reaction with $AlCl_3$ gave a 1:1 mixture of IVa and Va. Condensation of 4-t-butyl-2-formyltoluene (IIIa) with IVa in the usual manner afforded the



corresponding chalcone derivative VIa which was easily reduced by hydrogenation in the presence of PtO_2 catalyst to VIIa. Reduction of VIIa

with $LiAlH_4/AlCl_3$ system in ether afforded the desired compound VIIIa in good yield; this method also allowed the preparation of VIIIb from Ib.

EXPERIMENTAL SECTION

Preparation of 2-Acetyl-4-t-butyltoluene (IVa).- To a suspension of 1.2 g (7.42 mmol) of ferric chloride in 10 ml of carbon tetrachloride at 0-5°, was added 0.58 g (7.42 mmol) of acetyl chloride with stirring. Then, 1.0 g (6.75 mmol) of Ia in 3 ml of carbon tetrachloride was added; stirring was continued for 2 hrs at 0-5°. The reaction mixture was poured into a large amount of water and extracted with dichloromethane. The dichloromethane extract was washed with brine and water, dried over sodium sulfate and evaporated in vacuo to leave a residue which was distilled under reduced pressure to afford 0.98 g (76%) of IVa as pale yellow oil, bp. 80°/0.8 mm, lit.[2] 150°/20 mm. IR (neat): 1680 cm^{-1}. NMR ($CDCl_3$): δ 1.32 (9H, s), 2.46 (3H, s), 2.57 (3H, s), 7.10 (1H, d, J = 8.0 Hz), 7.35 (1H, dd, J = 8.0 Hz, 2.0 Hz), 7.62 (1H, d, J = 2.0 Hz). Although formation of Va was detected by glc, it could not be isolated.

Preparation of 5,5'Di-t-butyl-2,2'-dimethylchalcone (VIa).- A solution of 3.56 g (20.2 mmol) of IIIa, 3.84 g (20.2 mmol) of IVa and 1.05 g (26.3 mmol) of NaOH in 5 ml of ethanol and 5 ml of water was stirred vigorously for 96 hrs at room temperature. To the reaction mixture was added a large amount of water and extracted with dichloromethane. The dichloromethane extract was washed with water, dried and evaporated in vacuo to give 5.59 g (79%) of VIa, as yellow oil, bp. 250°/1.5 mm.

Anal. Calcd for $C_{25}H_{32}O$: C, 86.16; H, 9.25

Found: C, 86.35; H, 9.32

IR(neat): 1645 cm^{-1}; NMR ($CDCl_3$): δ 1.32 (18H, s), 2.31, 2.40 (each 3H, s), 6.90-7.90 (8H, m). Mass: m/e 348 (M^+).

Preparation of 1,3-Bis(5-t-butyl-2-methylphenyl)-1-propanone (VIIa).- A

solution of 5.53 g (15.9 mmol) of VIa in 50 ml of ethanol was hydrogenated using hydrogen gas over 100 mg of PtO_2 with stirring for 17 hrs at room temperature. To the reaction mixture was added dichloromethane, and the inorganic materials were filtered. The filtrate was concentrated to give 4.69 g (84%) of VIIa, as pale yellow liquid, bp. 210°/1.5 mm.

Anal. Calcd for $C_{25}H_{34}O$: C, 85.66; H, 9.78

Found: C, 85.78; H, 9.72

IR (neat): 1680 cm^{-1}. NMR ($CDCl_3$): δ 1.28, 1.29 (each 9H, s), 2.27, 2.43 (each 3H, s), 2.80-3.30 (4H, m), 6.90-7.60 (6H, m). Mass: m/e 350 (M^+).

Preparation of 1,3-Bis(5-t-butyl-2-methylphenyl) propane (VIIIa).- To a suspension of 1.50 g (39.6 mmol) of $LiAlH_4$ in 15 ml of dry ether was added with stirring 5.29 g (39.6 mmol) of $AlCl_3$ in 20 ml of dry ether at room temperature. Then, 4.63 g (13.2 mmol) of VII in 20 ml of dry ether was added with stirring and the mixture was boiled under reflux for 12 hrs. The etheral solution was then poured into a mixture of ice and dil. hydrochloric acid, separated and washed with water several times. The ethereal solution was then dried over Na_2SO_4 and concentrated; the product was purified by filtration through silica gel with hexane to give 1.37 g (95%) of VIIIa, as pale yellow liquid, bp. > 250°/6 mm., lit.[1] bp. > 250°/6 mm.

Preparation of IIb.- To a mixture of 51 g (0.31 mol) of Ib,[3] a small amount of iron powder and 40 ml of CCl_4 was added gradually a solution of 55 g (0.34 mmol) of bromine in 26 ml of CCl_4 at 5-6° within 1 hr. After the reaction mixture had been stirred for 1 hr at room temperature, it was poured into cold 10% NaOH solution (200 ml) and extracted with dichloromethane. The dichloromethane extract was washed with water, dried over $MgSO_4$ and evaporated in vacuo to give a residue which was distilled and afforded 52 g (70%) of IIb as colorless oil, bp. 101-104°/1 mm, lit.[3]

101-103°/1 mm.

Preparation of IIIb.- To a suspension of 4.70 g (0.19 g.-atom) of Mg powder in 5 ml of ether was added dropwise a solution of 47.1 g (0.17 mol) of IIb in 150 ml of ether under a stream of nitrogen. The reaction mixture was refluxed for 4 hrs in the presence of a pinch of a iodine. To the ethereal solution was added 32 g (0.22 mol) of ethyl orthoformate. After 17 hrs of reflux, the solvent was evaporated in vacuo to leave a residue to which dil. HCl solution was added until the organic layer separated. The organic layer was extracted with ether and the ethereal solution was washed with water, dried over Na_2SO_4 and evaporated in vacuo to leave a residue which was distilled under reduced pressure to afford 20.6 (62%) of IIIb as a colorless oil, bp. 115-117°/2.5 mm; IR (neat): 1680 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.28 (9H, s), 3.88 (3H, s), 5.26 (1H, s), 6.88 (1H, d, J = 8 Hz), 7.55 (1H, dd, J = 8 Hz, 3 Hz), 7.80 (1H, d, J = 3 Hz).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39

Found: C, 74.54; H, 8.59

Preparation of IVb.- To a solution of 30 g (0.18 mol) of Ib and 30 g (0.33 mol) of acetic anhydride in 250 ml of CCl_4 was added dropwise a solution of 200 g of $TiCl_4$ in 200 ml of CCl_4 at 0° within 1.5 hr. After stirring for 3.5 hrs at room temperature, the reaction mixture was poured into a large amount of ice-water and extracted with dichloromethane. The dichloromethane extract was washed with water, dried over $MgSO_4$ and evaporated in vacuo to leave a residue which was distilled under reduced pressure to afford 26 g (70%) of IIIb as colorless oil, bp. 109-116°/1 mm, IR (neat): 1670 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.28 (9H, s), 2.59 (3H, s), 3.86 (3H, s), 6.87 (1H, d, J = 9 Hz), 7.46 (1H, dd, J = 3 Hz, 9 Hz), 7.72 (1H, d, J = 3 Hz).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80

Found: C, 75.52; H, 8.59

Preparation of VIb.- To a solution of 9.6 g (50 mmol) of IIIb, 2.6 g (65 mmol) of sodium hydroxide in 15 ml of ethanol was added dropwise 10.3 g (50 mmol) of IVb in 15 ml of ethanol at room temperature; after 48 hrs, the organic layer was poured into a large amount of water and extracted with dichloromethane. The dichloromethane solution was washed with water, dried over Na_2SO_4 and evaporated in vacuo to afford 13.9 g (73%) of VI as pale yellow viscous oil. IR (neat): 1650 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.31 (18H, s), 3.82 (3H, s), 3.85 (3H, s), 7.76-7.98 (8H, m).

Compound VIb was used for preparation of VIIb without further purification since its purification was very difficult.

Preparation of VIIb.- Through a solution of 11 g (29 mmol) of VIb in 70 ml of ethanol in the presence of 100 mg of PtO_2 was bubbled hydrogen gas at room temperature for 24 hrs. The catalyst was filtered and the filtrate was evaporated in vacuo to give 11 g (nearly quantitative) of crude VIIb as colorless oil (containing about 25% of VIIIb), which was treated with a small amount of ethanol to give 8.25 g (75%) of pure VIIb as colorless crystals (EtOH), mp. 81-82°. ^{1}H-NMR ($CDCl_3$): δ 1.28 (9H, s), 1.29 (9H, s), 2.88-3.06 (2H, m), 3.18-3.36 (2H, m), 3.77 (3H, s), 3.82 (3H, s), 6.65-7.68 (6H, m).

Anal. Calcd for $C_{25}H_{34}O_3$: C, 78.49; H, 8.96

Found: C, 78.63; H, 8.91

Preparation of VIIIb.- To a suspension of 0.495 g (13.1 mmol) of $LiAlH_4$ in 10 ml of ether was gradually added a solution of 1.74 g (13.1 mmol) of $AlCl_3$ in 10 ml of ether. To this ethereal solution was then gradually added 0.5 g of VIIb in 20 ml of ether within 10 min. at room temperature. After the reaction mixture was stirred for 20 hrs, it was poured into dil. H_2SO_4 solution. The organic layer was extracted with dichloromethane; the organic extract was then washed with water, dried over sodium sulfate and

evaporated in vacuo to give 0.47 g (98%) of VIIIb as colorless plates (EtOH), mp. 61.5-63°. ^{1}H-NMR ($CDCl_3$): δ 1.28 (18H, s), 1.70-2.04 (2H, m), 2.68 (4H, m), 3.76 (6H, s), 6.68-6.77 (2H, m), 7.07-7.16 (4H, m).

Anal. Calcd for $C_{25}H_{36}O_2$: C, 81.47; H, 9.85

Found: C, 81.44; H, 9.77

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A SIMPLE SYNTHESIS OF 3-(1-PYRROLYL) FLAVONOIDS

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Several new routes for the synthesis of 3-aminoflavanones and flavones and their N-alkylated derivatives developed earlier,[1-5] failed to afford 3-azolylflavonoids because of the low nucleophilicity of the azole system. Recently, a modified method[6,7] reported for the preparation of 1H-pyrroles prompted us to utilize this reaction for the synthesis of the hitherto unknown 3-(1-pyrrolyl)flavanones (3) and flavones (6 and 7).