A New Route for the Preparation of 10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene Using Friedel–Crafts Intramolecular Cyclobenzylation

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A convenient preparation of 10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cycloheptene based on a novel Friedel–Crafts intramolecular cyclobenzylation, involving five steps from 1,2-diphenylethane, is described.

10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (**7**) has been of interest pharmacologically as an antiinflammatory[1] and antidepressant[2] drug. However, there were only two reported synthesis available,[3,4] which although starting from readily available materials, are too lengthy for practical purposes.

We have previously reported a convenient preparation of 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (**7**) from diphenylmethane, by using a *tert*-butyl group as a positional protecting function.[5] However, to construct the seven-membered ring, the sulfur ring contraction of 3,9-di-*tert*-butyl-7,12-dihydro-5*H*-dibenzo[*c*,*f*]thiocin, which was prepared from 4,4′-di-*tert*-butyl-2,2′-bis(chloromethyl)diphenylmethane with sodium sulfide in methanol under high dilution conditions, was necessary.

We now report a more convenient preparation of **7** in five steps from a readily available starting compound, 1,2-diphenylethane (**1**) involving a novel Friedel–Crafts intramolecular cyclobenzylation and use of *tert*-butyl group as a positional protecting group. The preparation of 1,2-bis(4-*tert*-butylphenyl)ethane (**3**) was described in a previous report.[6] Treatment of **3** with α,α-dichloromethyl methyl ether in dichloromethane in the presence of titanium(IV) chloride at 0 °C, gave the expected 2-(4-*tert*-butylphenethyl)-5-*tert*-butylbenzaldehyde (**4**) in 93% yield. The reduction of **4** with lithium aluminum hydride in diethyl ether afforded 2-hydroxymethyl derivative **5** in 71% yield. Recently we found that Nafion-H®, a perfluorinated resin sulfonic acid, catalyzes Friedel–Crafts benzylation of benzene and substituted benzenes with benzyl alcohols under relatively mild conditions.[7] Treatment of **5** with a catalytic amount of Nafion-H® (30 wt%) in refluxing dichloromethane gave, surprisingly, the intramolecular cyclobenzylation product **6** in 95% yield. This cyclization reaction was much faster in refluxing benzene or toluene solution (within 30 min). However, no concomitant *trans-tert*-butylation was observed using these reaction conditions.[8] The aluminum chloride/nitromethane catalyzed *trans*-alkylation of **6** in benzene afforded the desired 10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cycloheptene (**7**) in 90% yield together with formation of *tert*-butylbenzene (**8**).

Utilizing this reaction we have developed a one-pot procedure to convert 2-(4-*tert*-butylphenethyl)-5-*tert*-butylbenzyl alcohol (**5**) directly to 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (**7**) more conveniently. Thus, treatment of **5** with aluminum chloride/nitromethane catalyst in benzene at 50 °C for 4 h afforded **7** in 85% yield. Consequently, the preparative route to compound **7** can be shortened to four steps from 1,2-diphenylethane (**1**).

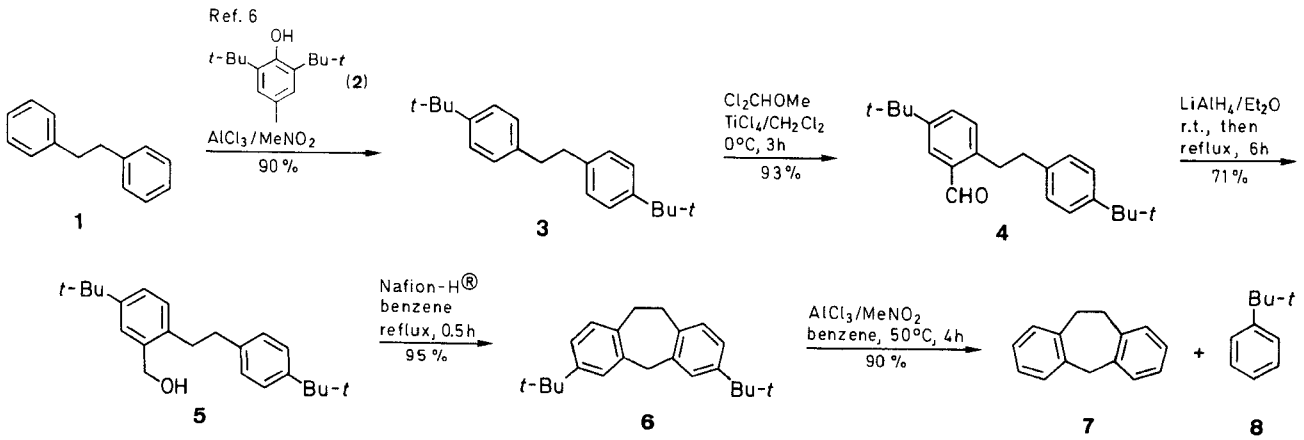
The presently developed method appears to be more practical for the preparation of **7** than the reported methods. The scope and limitation of Friedel–Crafts intramolecular cyclobenzylation reaction to give dibenzocycloalkanes is now under study.

2-(4-*tert*-Butylphenethyl)-5-*tert*-butylbenzaldehyde (4):
To a solution of 1,2-bis(4-*tert*-butyldiphenyl)ethane[6] (**3**) (1.0 g, 3.7 mmol) and Cl_2CHOMe (1.5 mL) in CH_2Cl_2 (40 mL) is added a solution of $TiCl_4$ (1.5 mL) in CH_2Cl_2 (10 mL) at 0 °C. After the mixture has been stirred for 3 h, it is poured into ice-water, extracted with CH_2Cl_2 (50 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give **4** as colorless prisms; yield: 1.02 g (93%); mp 61–63 °C (from hexane).

$C_{23}H_{30}O$ (322.5) calc. C 85.66 H 9.38
found 85.50 9.20

IR (KBr): ν = 2960, 2865, 1706, 1608, 1496 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.32 (s, 9 H), 1.35 (s, 9 H), 2.82–2.88 (m, 2 H), 3.24–3.30 (m, 2 H), 7.19–7.34 (m, 5 H), 7.56 (dd, 1 H, J = 2.0, 8.3 Hz), 7.85 (d, 1 H, J = 2.0 Hz), 10.25 (s, 1 H).



2-(4-*tert*-Butylphenethyl)-5-*tert*-butylbenzyl Alcohol (5):
To a suspension of $LiAlH_4$ (1.46 g, 38.5 mmol) in Et_2O (10 mL) is added a solution of **4** (2 g, 6.20 mmol) in Et_2O (45 mL) at r.t. After the mixture has been refluxed for 6 h, it is poured into ice-water, extracted with Et_2O (50 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give **5** as colorless prisms; yield: 1.41 g (71%); mp 88–90°C (from hexane).

$C_{23}H_{32}O$	calc.	C 85.13	H 9.94
(324.5)	found	85.14	9.89

IR (KBr): ν = 3393, 3055, 2958, 1516, 1461, 1411, 1035, 823 cm^{-1}.

MS (*m/z*): 324 (M^+).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.22 (s, 9 H), 1.23 (s, 9 H), 2.78–2.82 (m, 4 H), 3.40 (s, 1 H), 4.54 (s, 2 H), 7.08–7.30 (m, 7 H).

3,7-Di-*tert*-butyl-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene (6):
After a mixture of **5** (1.0 g, 3.10 mmol) and Nafion-H® (300 mg) in benzene (30 mL) is refluxed for 30 min, it is filtered off and the filtrate is evaporated *in vacuo* to give **6** as colorless prisms; yield: 0.93 g (95%); mp 160–162°C (from EtOH).

$C_{23}H_{30}$	calc.	C 90.13	H 9.87
(306.5)	found	90.10	9.80

IR (KBr): ν = 3050, 2962, 1506, 1458, 830 cm^{-1}.

MS (*m/z*): 306 (M^+).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.30 (s, 18 H), 3.04 (s, 4 H), 4.04 (s, 2 H), 6.90–7.22 (m, 6 H).

10,11-Dihydro-5*H*-dibenzo[*a,d*]cycloheptene (7):
To a solution of **6** (500 mg, 1.55 mmol) or **5** (503 mg, 1.55 mmol) in benzene (30 mL) is added a solution of $AlCl_3$ (785 mg, 5.90 mmol) in $MeNO_2$ (1.5 mL). After the mixture has been stirred for 4 h at 50°C, it is poured into ice-water, extracted with Et_2O (50 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give **7** as colorless prisms; yield 274 mg (90%) (from **6**), 256 mg (85%) (from **5**); mp 75–76°C (from EtOH) (Lit.[2] mp 78–79°C).

The formation of *tert*-butylbenzene **(8)** was confirmed by GC (conditions: Shimazu gas chromatography, GC-14A, Silicone OV-1, 2 m, programmed temperature rise, 12°C/min; carrier gas nitrogen, 25 mL/min).

Received: 6 February 1991

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