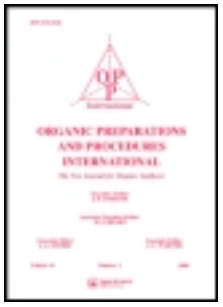


Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

A NEW ROUTE FOR THE PREPARATION OF XANTHENE DERIVATIVES USING FRIEDEL-CRAFTS INTRAMOLECULAR CYCLOBENZYLATION

Takehiko Yamato [a] , Masayasu Komine [a] & Yoshiaki Nagano [b]

[a] Department of Applied Chemistry, Faculty of Science and Engineering, Saga University, Honjo-machi 1, Saga-shi, Saga, 840, JAPAN

[b] Tohwa Institute of Science, Tohwa University, 1-1 Chikushigaoka, Minami-ku, Fukuoka, 815, JAPAN

Version of record first published: 09 Feb 2009.

To cite this article: Takehiko Yamato , Masayasu Komine & Yoshiaki Nagano (1997): A NEW ROUTE FOR THE PREPARATION OF XANTHENE DERIVATIVES USING FRIEDEL-CRAFTS INTRAMOLECULAR CYCLOBENZYLATION, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 29:3, 300-303

To link to this article: http://dx.doi.org/10.1080/00304949709355200

****

A NEW ROUTE FOR THE PREPARATION OF XANTHENE DERIVATIVES USING FRIEDEL-CRAFTS INTRAMOLECULAR CYCLOBENZYLATION†

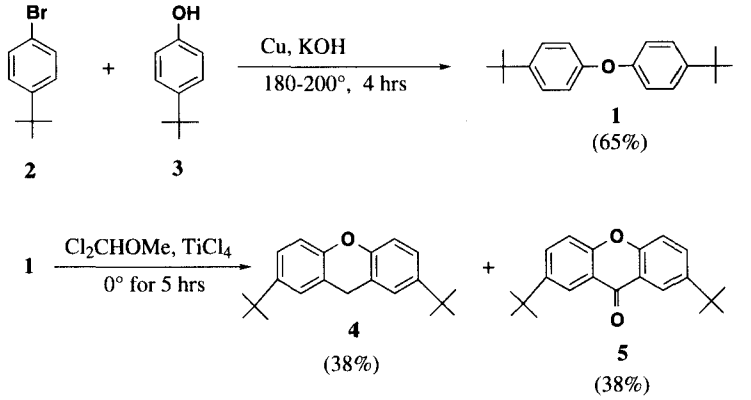
Submitted by (09/17/96)

Takehiko Yamato*, Masayasu Komine and Yoshiaki Nagano††

Department of Applied Chemistry, Faculty of Science and Engineering
Saga University, Honjo-machi 1, Saga-shi, Saga 840, JAPAN

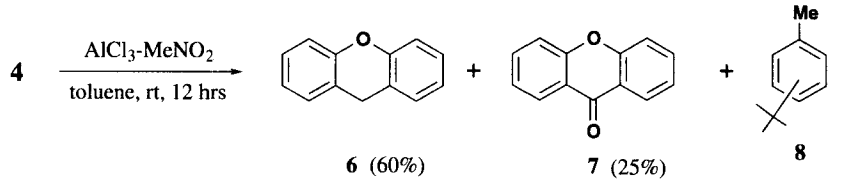
†† *Tohwa Institute of Science, Tohwa University*
1-1 Chikushigaoka, Minami-ku, Fukuoka 815, JAPAN

Although there are numerous syntheses of xanthenes from 2-mono- and 2,2'-disubstituted diphenyl ethers using a cyclization reaction,[1-3] there has not been any report concerning Friedel-Crafts intramolecular benzylation of 2-halomethyldiphenyl ethers to give xanthenes. This paper describes the first successful elaboration of a xanthene skeleton *via* Friedel-Crafts intramolecular benzylation by the action of dichloromethyl methyl ether and $TiCl_4$ on 4,4'-di-*tert*-butyldiphenyl ether (**1**), which is so constructed that electrophilic substitution occurs to *ortho* to the diphenyl ether linkage.



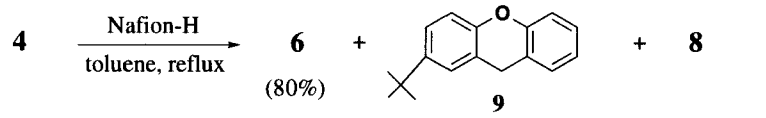
Coupling reaction of 4-*tert*-butylbromobenzene (**2**) and 4-*tert*-butylphenol (**3**) in the presence of KOH and copper at 180-200° for 4 hrs afforded **1** in 65% yield (Scheme 1). Treatment of **1** with 7.0 mol equiv. of Cl_2CHOMe in the presence of $TiCl_4$ at 0° for 5 hrs, 2,7-di-*tert*-butylxanthene (**4**) was obtained in 38% yield along with 2,7-di-*tert*-butylxanthone (**5**) in 38% yield. Further electrophilic substitution to 2,7-di-*tert*-butylxanthene (**4**) was not observed in the present system in spite of prolonged reaction time to 24 hrs. This finding might be attributable to the steric hindrance of *tert*-butyl groups on the xanthene ring, which prevents further substitution of electrophile. The structures of **4** and **5** were assigned on the basis of elemental analyses and spectral data. For instance, the mass spectral data for **4** and **5** (M^+ = 294 and 308) strongly supports xanthene and xanthone skeletons. The

IR spectrum of **5** shows the absorption of the carbonyl stretching vibration around 1661 cm^{-1} for the xanthone skeleton. The ^{1}H-NMR spectrum (in $CDCl_3$) of **4** exhibits a singlet for the *tert*-butyl protons (δ 1.31), a singlet for the C-9 methylene protons (δ 4.02) and a 1,2,4-trisubstituted pattern for the benzene ring protons. These observations and chemical conversion of **5** by hydroalane reduction to **4** strongly suggest that compound **4** is 2,7-di-*tert*-butylxanthene.



(1)

When 2,7-di-*tert*-butylxanthene (**4**) was treated with $AlCl_3$-$MeNO_2$ in toluene at room temperature for 12 hrs, the desired xanthene (**6**) was obtained in 60% yield along with a mixture of trans-*tert*-butylated xanthone (**7**) and *tert*-butyltoluenes (**8**).



(2)

trans-tert-Butylation of **4** in the presence of Nafion-H (200 wt%) as a catalyst in boiling toluene afforded **6** in 80% yield along with **8** and **9**. The present method provides good yields, easy isolation of the products, and no concomitant chlorination at 9-position of xanthene to afford xanthone were observed under the reaction conditions.

EXPERIMENTAL SECTION

All melting points are uncorrected. ^{1}NMR spectra were recorded on a Nippon Denshi JEOL FT-270 NMR spectrometer in $CDCl_3$ with TMS as an internal reference. IR spectra were measured as KBr pellets or as liquid films on NaCl plates in a Nippon Denshi JIR-AQ2OM spectrometer. Mass spectra were obtained on a Nippon Denshi JMS-01SA-2 spectrometer at 75 eV using a direct inlet system. 4-*tert*-Butylbromobenzene (**2**) was prepared by bromination of *tert*-butylbenzene with bromine in carbon tetrachloride in the presence of iron power at 0° for 1 hr in 84% yield. Nafion-H was prepared from commercially available (Du Pont) Nafion-K resin, as previous described.[4]

Preparation of 4,4'-Di-*tert*-butyldiphenyl Ether (1).- A mixture of 4-*tert*-butylphenol (**4**) (8.4 g, 120 mmol) and KOH (18 g, 120 mmol) was heated at 150° for 1 hr while stirring. To the reaction mixture was added 4-*tert*-butylbromobenzene (**2**) (22 g, 100 mmol) and then copper powder (80 mg) and heated at 180-200° for 4 hrs. The reaction mixture was cooled to room temperature and poured into a large amount of ice-water and extracted with CH_2Cl_2 (2 x 200 mL). The organic layer was washed with water (2 x 100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed over silica gel (Wako, C-300; 200 g) with a hexane as eluent to give **1** (19.1 g, 65.4%) as a colorless oil; NMR ($CDCl_3$): δ 1.36 (18 H, s), 6.93 (4 H, d, *J* 8.8), 7.32 (4 H, d, *J* 8.8);

mass spectrum: *m/e* 282 (M^+).

Anal. Calcd. for $C_{20}H_{26}O$: C, 85.06; H, 9.28. Found: C, 85.39; H, 9.43

Reaction of 1 with Cl_2CHOMe.- To a solution of 4,4'-di-*tert*-butyldiphenyl ether (**1**) (1.0 g, 3.54 mmol) and Cl_2CHOMe (1.84 mL, 24.8 mmol) in CH_2Cl_2 (20 mL) was added a solution of $TiCl_4$ (3.26 mL, 28.4 mmol) in CH_2Cl_2 (5 mL) at 0°. After stirred at 0° for 5 hrs, it is poured into ice-water, extracted with CH_2Cl_2 (2 x 50 mL). The organic layer was washed with water (2 x 20 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford a mixture of **4** and **5** in the ratio 48:52 (NMR spectrum). The residue was chromatographed over silica gel (Wako, C-300; 100 g) with hexane and benzene as eluent to give **4** and **5**, respectively. Recrystallization of each fraction from methanol to afford **4** (400 mg, 38.4%) and **5** (416 mg, 38.1 %) as a colorless prisms, respectively. ***2,7-Di-tert-butylxanthene*** (**4**) was obtained as colorless prisms (methanol); mp. 157-161°. IR (KBr): 2957, 2904, 1491, 1482, 1401, 1305, 1289, 1257, 1180, 1115, 875 cm^{-1}; NMR ($CDCl_3$): δ 1.31 (18 H, s), 4.02 (2 H, s), 6.76 (2 H, d, *J* 8.3), 7.16 (2 H, d, *J* 2.4), (2 H, dd, *J* 2.4, 8.3); mass spectrum: *m/e* 294 (M^+).

Anal. Calcd. for $C_{21}H_{26}O$: C, 85.67; H, 8.90. Found: C, 85.42; H, 8.97

2,7-Di-*tert*-butylxanthone (**5**) was obtained as colorless prisms (methanol); mp. 161-163°. IR (KBr): 2963, 1661 (C=O), 1609, 1480, 1305, 1258 cm^{-1}; NMR ($CDCl_3$): δ 1.41 (18 H, s), 7.43 (2 H, d, *J* 8.8), 7.78 (2 H, dd, *J* 2.9, 8.8), 8.33 (2 H, d, *J* 2.9), ; mass spectrum: *m/e* 308 (M^+).

Anal. Calcd. for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.59; H, 7.85

Reduction of 5 with Hydroalane.- To a solution of hydroalane AlH_2Cl [prepared from $AlCl_3$ (5.25 g, 39.4 mmol) and $LiAlH_4$ (1.5 g, 39.4 mmol) in ether (20 mL)] was added a solution of **5** (2.1g, 6.82 mmol) in ether (100 mL) dropwise with gentle refluxing. After the reaction mixture had been refluxed for an additional 24 hrs, it was quenched with a cold aqueous 10% hydrochloric acid (50 mL) and extracted with ether (3 x 50 mL). The organic layer was washed with water (2 x 20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed over silica gel (Wako, C-300; 200 g) with a mixture of hexane and benzene (1:1) as eluent to give **4**. Recrystallization from methanol to afford **4** (1.63 g, 81.1%) as a colorless prisms.

$AlCl_3$-$MeNO_2$ Catalyzed *trans*-Alkylation of 4.- To a solution of **4** (200 mg, 0.68 mmol) in toluene (4 mL) was added a solution of $AlCl_3$ (264 mg, 1.98 mmol) in $MeNO_2$ (0.6 mL) at 0° and the mixture was stirred at room temperature for 24 hrs. The reaction mixture was poured into ice-water, extracted with CH_2Cl_2 (2 x 50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford a mixture of **6** and **7** in the ratio 69:31 (GLC analyses). The residue was chromatographed over silica gel (Wako, C-300; 50 g) with hexane and benzene as eluent to give **6** (74.4 mg, 60%) and **7** (33.4 mg, 25%) as colorless solids, respectively.

***Nafion-H Catalyzed trans-Alkylation of* 6.**- A solution of **6** (200 mg, 0.68 mmol) in toluene (4 mL) and Nafion-H (400 mg) was refluxed under nitrogen for 24 hrs. After the reaction mixture was cooled to room temperature, it was filtered and the filtrate was concentrated. The residue was chromatographed over silica gel (Wako, C-300; 50 g) with hexane as eluent to give a colourless solid, which was recrystallized from methanol to afford **6** (100 mg, 80%) as colorless prisms, mp. 101-105°,

lit.[1b] 101-102°.

REFERENCES

† Polycyclic Aromatic Hydrocarbons, Part 7. Part 6: T. Yamato, M. Fujimoto, Y. Nagano, A. Miyazawa and M. Tashiro, *Org. Prep. Proced. Int.*, **29**, 321 (1997).

1. a) A. A. Goldbergand and A. H. Wragg, *J. Chem. Soc.*, 4823 (**1957**); b) G. Metz, *Synthesis*, **1972**, 612.

2. A. Factor, H. Finkbeiner, R. A. Jerussi and D. M. White, *J. Org. Chem.*, **35**, 57 (1970).

3. a) P. Wan and C.-G. Huang, *Chem. Commun.*, 1193 (**1988**); b) C.-G. Huang and P. Wan, *J. Org. Chem.*, **56**, 4846 (1991).

4. a) G. A. Olah, P. S. Iyer and G. K. S. Prakash, *Synthesis*, 513 (**1986**); b) T. Yamato, *J. Synth. Org. Chem. Jpn*, **53**, 487 (1995) and references therein.

****

SYNTHESIS OF (*1R,cis*)-2-(3-AMINO-2,2-DIMETHYLCYCLOBUTYL)ETHANOL, A PRECURSOR OF CYCLOBUTANE CARBOCYCLIC NUCLEOSIDES

Submitted by (09/23/96)

José E. R. Borges, Franco Fernández, Xerardo García, Antonio R. Hergueta and Carmen López*

Departamento de Química Orgánica, Facultade de Farmacia
Universidade de Santiago, 15706-Santiago de Compostela, SPAIN

Carbocyclic analogues of nucleosides (CANs) can exhibit interesting antiviral[1] and antineoplastic[2] properties, and much of the recent work on these compounds has been in connection with the search for effective anti-HIV agents (for example, Carbovir (**1**) and Cyclobut-G (**2**) have shown promise as treatments of AIDS).[3] Synthesis of CANs generally involves construction of the purine or pyrimidine base about an appropriate amino alcohol, which in the case of Cyclobut-G is compound **3**.[4] As part of a research program to examine the effect of the structural and configurational features of the amino alcohol moiety on the antiviral activity of CANs, we required amino alcohol **9**. Herein we