

NEW SYNTHESIS OF CYPROHEPTADINE AND RELATED COMPOUNDS USING LOW VALENT
 TITANIUM

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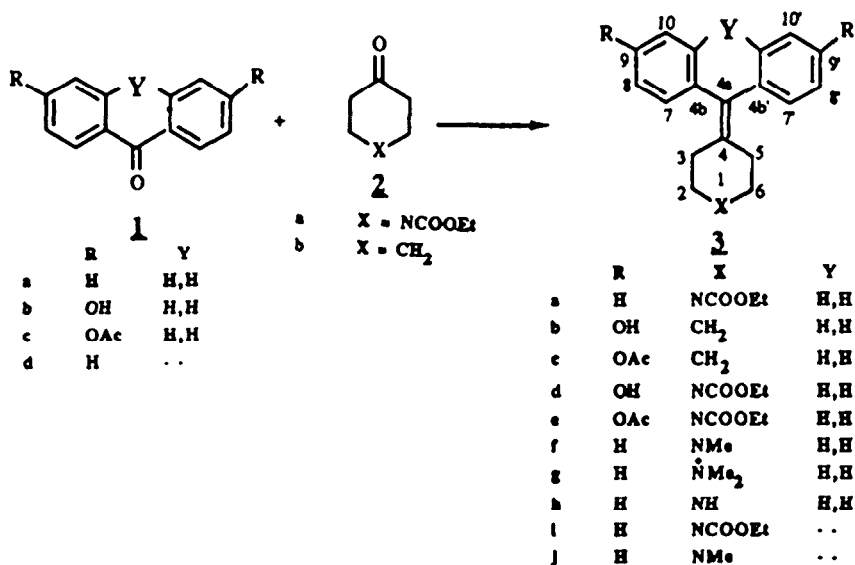
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(Received in UK 19 July 1988)

Abstract: A simple method is described for the preparation of biphenylmethylenepiperidine, cyproheptadine and related compounds based on asymmetric dicarbonyl coupling of two suitable ketones with low valent titanium.

Antihistamine drugs, such as biphenylmethylenepiperidine, cyproheptadine and related compounds, have been used widely in the treatment of allergic diseases. Up to now the synthesis of these compounds has been achieved by classical methods.^{1,2}

In this paper we describe a new direct synthesis of biphenylmethylenepiperidine (3f), cyproheptadine (5b) and related compounds which is based on the application of low valent titanium reductive dicarbonyl coupling³ of two suitable ketones in order to form the exocyclic double bond characteristic of these compounds.



Scheme 1

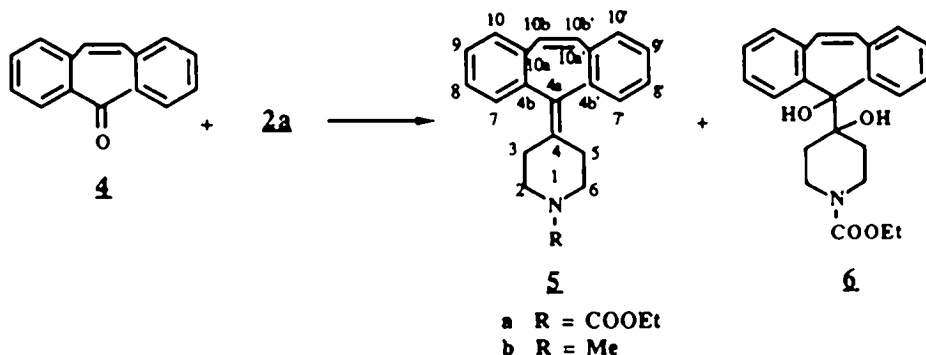
The synthesis of biphenylmethylenepiperidine (3f) was carried out by treatment of an equimolar mixture of benzophenone (1a) and N-carboxy-4-piperidone (2a), both of which are cheap and easily available, with low

valent titanium generated by reduction of $TiCl_3$ with lithium in refluxing DME. The *N*-carboxy derivative **3a** was obtained in 93% yield, and reduction of **3a** with $LiAlH_4$ afforded in 93% yield, the *N*-Me derivative **3f**, which was easily transformed by treatment with iodomethane into its dimethyl quaternary salt **3g**, which is known to be a parasymphathetic blocking agent.¹

The reductive coupling of 4,4'-dihydroxybenzophenone (**1b**) and cyclohexanone (**2b**) in the above conditions afforded **3b** in 87% yield. Compound **3b**, which possesses high ovulation inducing activity,² was easily transformed by acetylation into cyclofenil (**3c**), a lactant inhibitor.⁵

The preparation of the potent antihistamine and antiserotonin agent cyproheptadine (**5b**)² was carried out by coupling suberenone (**4**) with *N*-carboxy-4-piperidone (**2a**), which afforded the urethane **5a** in 18% yield. The major product (66%) was **6**, whose structure was deduced from spectroscopic data and confirmed by its synthesis according to the procedure described by E.J.Corey.⁶ We attributed the formation of **6** to incomplete deoxygenation, so we raised the molar carbonyl compound: $TiCl_3$ ratio from 1:4 to 1:6 which improved the yield of compound **5a** to 60%. Compound **5a** was easily reduced with $LiAlH_4$ to give cyproheptadine (**5b**) in quantitative yield.

Recent studies of cyproheptadine related compounds suggest that the presence of a *N*-carboxy function on the nitrogen atom, instead of a methyl group, removes side effects on the central nervous system while retaining antihistamine activity.⁷ Our new synthetic method provides a direct route to this sort of compounds.



Scheme 2

EXPERIMENTAL PART

All melting points are uncorrected. Proton and carbon nmr spectra were obtained on a Bruker WM-250 (250MHz), using $CDCl_3$ as solvent and TMS as internal standard, all signals are expressed as δ values ppm downfield from TMS. Mass spectra were recorded with a Kratos MS-25 Instrument at 70eV ionizing energy. IR spectra were recorded with a PYE UNICAM 1100 spectrometer. Thin layer chromatography (tlc) was performed on analytical plates coated with GF₂₅₄(type 60) silica gel (from Merck). Elemental analyses were carried out in a PELKIN ELMER 240-B Instrument.

Dried solvents were distilled under argon from sodium benzophenone ketyl radical immediately prior to use.

4,4'-diacetoxybenzophenone (1c)

4,4'-dihydroxybenzophenone (**1b**) (1g, 4.7mmol) was dissolved in dry pyridine (5ml) and treated with acetic anhydride (3ml, 29mmol). The mixture was kept at room temperature for 6 hours. The solvent was evaporated under reduced pressure and the residue was taken into dichloromethane, washed with dilute hydrochloric acid, dried over sodium sulphate and concentrated to give 4,4'-diacetoxybenzophenone (**1c**) (1.4 g, 4.6mmol) which was recrystallized from methanol as white crystals (m.p.157°C). NMR (¹H): 7.85 (d, J=8.0Hz, 4H, ArH); 7.22 (d, J=8.0Hz, 4H, ArH); 2.34 (s, 6H, 2 x COCH₃).

General Procedure for Mixed Carbonyl Coupling Using $TiCl_3$ /Li

Lithium pieces (342mg, 49mmol) were added to a stirred slurry of $TiCl_3$ in 80 ml of dry DME under an argon atmosphere and the mixture was refluxed for 2 hours. The black slurry was then cooled to room temperature

argon atmosphere and the mixture was refluxed for 2 hours. The black slurry was then cooled to room temperature and the two carbonyl compounds (1.75 mmol of each) dissolved in 10 ml of dry DME were added. The mixture was stirred for 4 hours at room temperature and then refluxed for 13 hours. After cooling at room temperature, the reaction mixture was filtered, a saturated aqueous solution of K_2CO_3 added, the organic layer separated and the aqueous layer extracted with chloroform (3 x 50 ml). The pooled organic phases were dried (Na_2SO_4) and the solvent was evaporated to afford the crude product. This procedure was used for the following reactions.

1.-Synthesis of 3a

Benzophenone (1a) with 1 equiv. of N-carbethoxy-4-piperidone (2a) gave 3a in 93% yield as white crystals (m.p.125°C, methanol-hexane). NMR (1H): 7.32-7.09 (m, 10H, ArH); 4.13 (q, J=7.1Hz, 2H, OCH_2CH_3); 3.49 (t, J=5.8Hz, 4H, NCH_2); 2.34 (t, J=5.8Hz, 4H, CCH_2); 1.25 (t, J=7.1Hz, 3H, OCH_2CH_3). Anal.: found C 78.36; H 6.99; N 4.42; calculated for $C_{21}H_{23}NO_2$ C 78.50; H 7.16; N 4.36.

2.-Synthesis of 3i

Fluorenone (1d) with 1 equiv. of N-carbethoxy-4-piperidone (2a) gave 3i in 70% yield as yellow crystals (m.p.116°C, methanol-hexane). NMR (1H): 7.80 (m, 4H, ArH); 7.32 (m, 4H, ArH); 4.21 (q, J=7.1Hz, 2H, OCH_2CH_3); 3.72 (m, 4H, NCH_2); 3.33 (t, J=6.1Hz, 4H, CCH_2); 1.21 (t, J=7.1Hz, 3H, OCH_2CH_3). Anal.: found C 79.02; H 6.75; N 4.28; calculated for $C_{21}H_{21}NO_2$ C 79.00; H 6.58; N 4.39.

3.-Synthesis of 3d

4,4'-dihydroxybenzophenone (1b) with 1 equiv. of N-carbethoxy-4-piperidone (2a) and $TiCl_3$ (2.7g, 1.7mmol) gave 3d in 53% yield as white crystals (m.p.105°C, chloroform). NMR (1H): 7.09 (d, J=8.6Hz, 2H, ArH); 6.94 (d, J=8.5Hz, 2H, ArH); 6.75 (d, J=8.6Hz, 2H, ArH); 6.75 (d, J=8.5Hz, 2H, ArH); 4.15 (m, 2H, OCH_2CH_3); 3.47 (m, 4H, NCH_2); 2.33 (m, 4H, CH_2); 1.26 (t, J=7.1Hz, 3H, OCH_2CH_3). (^{13}C): 157.23 (C=O), 135.27, 133.08, 131.92 and 129.98 (C4a, C4b, C4b', C7, C7', C11, C11', C8, C8', C10, C10'), 115.84 (C9, C9'), 62.65 (OCH_2CH_3), 45.11 (C6, C2), 32.56 (C5, C3), 14.91 (OCH_2CH_3). MS: m/e(%) 353(67), 251(28), 237(23), 199(100). Anal.: found C 71.16; H 6.88; N 4.27; calculated for $C_{21}H_{23}NO_4$ C 71.38; H 6.52; N 3.97.

5.-Synthesis of 3e

4,4'-diacetoxybenzophenone (1c) with 1 equiv. of N-carbethoxy-4-piperidone (2a) and $TiCl_3$ (1.08g, mmol) gave 3e (82%) as white crystals (m.p.107°C, chloroform). NMR (1H): 7.08 (d, J=8.7Hz, 4H, ArH); 6.99 (d, J=8.7Hz, 4H, ArH); 4.10 (q, J=7.1Hz, 2H, OCH_2CH_3); 3.46 (m, 4H, NCH_2); 2.32 (m, 4H, CH_2); 2.26 (s, 6H, 2 x $COCH_3$); 1.23 (t, J=7.1Hz, 3H, OCH_2CH_3). MS: m/e(%) 395(100), 353(92), 251(83), 237(41).

6.-Synthesis of 3b and 3c

4,4'-dihydroxybenzophenone (1b) with 1 equiv. of cyclohexanone (2c) and $TiCl_3$ (2.7g, 1.7mmol) gave 3b (87%) as white crystals (m.p.241°C, dichloromethane-methanol). NMR (1H): 6.97 (d, J=9.0Hz, 4H, ArH); 6.72 (d, J=9.0Hz, 4H, ArH); 2.22 (m, 4H, CH_2); 1.37 (m, 6H, CH_2); 1.56 (bs, OH). Anal.: found C 80.85; H 7.21; calculated for $C_{19}H_{20}O_2$ C 81.13; H 7.47

As above, 3b was treated with acetic anhydride and pyridine to yield 3c quantitatively as white crystals (m.p.138°C, chloroform-methanol). NMR (1H): 7.15 (d, J=9.0Hz, 4H, ArH); 6.98 (d, J=9.0Hz, 4H, ArH); 2.15 (s, 6H, 2 x $COCH_3$); 2.21 (m, 4H, CH_2); 1.35 (m, 6H, CH_2). Anal.: found C 76.08; H 6.87; calculated for $C_{23}H_{24}O_4$ C 75.82; H 6.60

7.-Synthesis of 5a

Dibenzo(a,d)cyclohept-5-one (4) with 1 equiv. of N-carbethoxy-4-piperidone (2a) and $TiCl_3$ (12 equiv.) gave two products. The less polar, obtained as white crystals in 60% yield, was identified as 5a (m.p.116°C, methanol). NMR (1H): 7.15-7.36 (m, 8H, ArH); 6.91 (s, 2H, HC=CH); 4.12 (t, J=7.1Hz, 2H, OCH_2CH_3); 3.63 (m, 2H, H5 and H3); 3.10 (m, 2H, H5 and H3); 2.17 and 2.25 (m, 4H, H2 and H6); 1.25 (t, J=7.1Hz, 3H, OCH_2CH_3); (^{13}C): 155.52 (C=O), 138.79 (C4), 134.87, 134.72 and 134.4 (C4a, C4b, C4b', C10a', C10a), 130.00 (C10b, C10b'), 128.28, 128.22, 127.88 and 126.43 (C7, C7', C8, C8', C9, C9', C10, C10'), 61.18 (OCH_2CH_3), 45.19 (C2, C6), 29.88 (C3, C5), 14.56 (OCH_2CH_3). MS: m/e(%) 345(100), 316(24), 229(53). Anal.: found C 79.80; H 6.38; N 3.85; calculated for $C_{23}H_{23}NO_2$ C 80.00; H 6.67; N 4.06. The more polar compound was 6 (white crystals, m.p.179°C, ether-dichloromethane). IR: 1670, 3400 cm^{-1} . RMN: (1H) 8.06 (d, J=8.0Hz, 2H, ArH); 7.46-7.31 (m, 6H, ArH); 6.76 (s, 2H, HC=CH); 4.03 (q, J=7.1Hz, 2H, OCH_2CH_3); 3.82 (m, 4H, CH_2); 2.84 (m, 2H, CH_2); 1.40 (m, 2H, CH_2); 1.15 (t, J=7.1Hz, 3H, OCH_2CH_3). Anal.: found C 72.69; H 6.78; N 3.65; calculated for $C_{23}H_{25}NO_4$ C 72.80; H 6.60; N 3.69.

General Procedure for Reduction with Lithium Aluminium Hydride.

To a stirred solution of the corresponding N-carbethoxy compound (0.44 mmol) in 25 ml of dry THF, 2.2 equiv. of lithium aluminium hydride were added under argon. The solution was refluxed for two hours. After cooling at room temperature, a saturated solution of NH_4Cl was added, the solvent was evaporated and the mixture was

extracted with dichloromethane. The organic layer was separated and the solvent eliminated under vacuum to give the corresponding N-methyl compound.

1.-Compound 3f was obtained as an oil (93%). NMR (^1H): 7.32-7.09 (m, 10H, ArH); 2.68 (t, J=5.9Hz, 4H, NCH₂); 2.57 (t, J=5.9Hz, 4H, CCH₂); 2.45 (s, 3H, NMe).

2.-Compound 3j was prepared from 3i in 90% yield. NMR (^1H): 7.74-7.20 (m, 8H, ArH); 2.64-1.99 (m, 8H, CH₂), 2.23 (s, 3H, NMe).

3.-Compound 5b was obtained quantitatively from 5a as white crystals (m.p.110°C, chloroform-methanol). NMR (^1H): 7.10-7.25 (m, 8H, ArH); 6.92 (s, 2H, HC=CH); 2.06-2.55 (m, 8H, CH₂); 2.23 (s, 3H, NMe).

Formation of the Methiodide 3g

Methyl iodide (3 ml) was added to a solution of 3f (10 mmol) in acetone and the mixture was stirred overnight at room temperature. The methiodide precipitated quantitatively as a yellow solid (m.p.249°C, acetone). NMR (^1H): 7.35-7.13 (m, 10H, ArH); 3.72 (t, J=8.0Hz, 4H, CH₂); 3.56 (s, 6H, 2 x Me); 2.72 (t, J=8.0Hz, 4H, CH₂).

Synthesis of 3h

Potassium hydroxide (6.3g) was dissolved in absolute ethanol (30ml) by heating under argon. Compound 3a (430mg, 1.34mmol) was then added to the mixture and the solution was refluxed for 5.5 hours under argon. The solvent was evaporated, water (20ml) was added and the aqueous mixture was extracted with dichloromethane (3 x 50ml). The dried (Na₂SO₄) organic extracts were concentrated under vacuum, and the residue was purified by preparative tlc to yield 287 mg (86%) of 3h (m.p.84°C, methanol-ether). NMR (^1H): 7.09 (m, 10H, ArH); 2.86 (t, J=5.3Hz, 4H, NCH₂); 2.53 (m, 1H, N-H); 2.30 (t, J=5.3Hz, 4H, CCH₂).

ACKNOWLEDGEMENT

We thank the Comisión Asesora for financial support.

REFERENCES

- 1.- F. J. Villani, N. Sperberg, M. Sherlock, D. Papa, *J.Am.Chem.Soc.*, **73**, 5010 (1951)
- 2.- E. L. Engelhardt, H. C. Zeitl, W. S. Saari, M. E. Christy, C. D. Colton, C. A. Stone, J. M. Starvosky, H. C. Wenger, C. T. Ludden, *J.Med.Chem.*, **829** (1965)
- 3.- J. A. Seijas, A. R. de Lera, M. C. Vilaverde, L. Castedo, *J.Chem.Soc., Chem.Comm.*, **839** (1985)
- 4.- Y. Hiramatsu, A. Izumi, K. Miyasaka, H. Takahashi, M. Mieda, M. Tarutani, K. Nakanowatari, *Oyo Yakuri*, **1045** (1972). *C.A.* **78**, 131963z (1973)
- 5.- M. Cingotti, G. Magnin, *Rev. Fr. Gynecol. Obstet.*, **369** (1986). *C. A.* **105**, 183725u (1986)
- 6.- E. J. Corey, R. L. Danheiser, S. Chandrasekaran, *J.Org.Chem.*, **41**, 260 (1976)
- 7.- F. J. Villani, C. V. Magatti, D. B. Vashi, J. Wong, T. L. Popper, *Arzeim.-Forsch./Drug Res.*, **36**(II), 1311, (1986).