Tetrahedron Vol. 49, No. 6, pp. 1251-1256, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

SYNTHESIS OF APOMORPHINE ANALOGUES BY THE INTERMOLECULAR BENZYNE CYCLOADDITION (IBC) APPROACH

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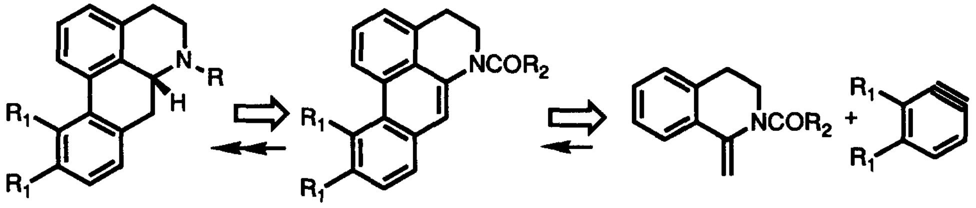
(*Received in UK* 23 *November* 1992)

Summary. A highly convergent, regioselective synthesis of apomorphine analogues is described. It relies on the intermolecular cycloaddition between a 1-methylene-1,2,3,4-tetrahydroisoquinoline and an asymmetrically substituted aryne.

Since the structural relationship between apomorphine (**1a**) and the neurotransmitter dopamine was realized, a large number of structure-activity studies of apomorphine analogues have been carried out. This has led to the development of several clinically useful drugs,[1]including N-propylnorapomorphine (**1b**), a dopaminergic agonist[2] with significantly greater activity than apomorphine itself.

Apomorphine analogues are usually prepared either from apomorphine itself, which is synthesized *de novo* by classical methods such as Pschorr cyclization, oxidative coupling of phenol (or phenol ethers) or photocyclization of appropriate precursors or by partial synthesis from aporphines[1]. However, these are in many cases lengthly and/or inconvenient procedures when compared with the recently developed Intermolecular Benzyne Cycloaddition (IBC) approach, i.e. the 4 + 2 intermolecular cycloaddition of styrene analogues and arynes. This versatile, convergent methodology has been successfully applied to the synthesis of dehydroaporphines, 4,5-dioxoaporphines and 7-oxoaporphines[3].

The use of this strategy for the synthesis of apomorphine analogues (Scheme 1) requires strict control of the regioselectivity of cycloaddition between the 1-methyleneisoquinolines **3** and the asymmetrically substituted arynes **4**, which *a priori* could lead to two isomers. The following is a full account of our investigations in this area which have led to a new route to apomorphine analogues.



1a R_1=OH, R=Me
1b R_1=OH, R=Pr

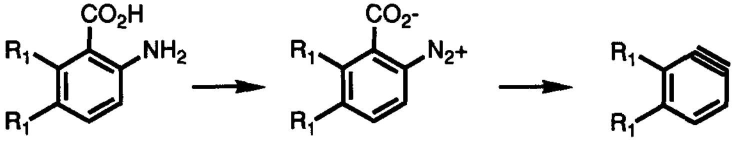
2a R_1=H, R_2=Me
2b R_1=H, R_2=Et
2c R_1=H, R_2=CF_3
2d R_1=OMe, R_2=Me

3a R_2=Me
3b R_2=Et
3c R_2=CF_3

4a R_1=H
4b R_1=OMe

Scheme 1

We were confident of reaching the basic apomorphine skeleton by regioselective cycloaddition between the N-protected 1-methylenetetrahydro-isoquinolines **3** and 3,4-dimethoxybenzyne (**4b**).[4] There was some concern, however, that ring-A-unsubstituted 1-methylene-1,2,3,4-isoquinolines might not be sufficiently polarized to undergo reaction. Therefore, as an initial test, compounds **3a**[5], **3b** and **3c** (all uneventfully prepared by treatment of 3,4-dihydro-1-methylisoquinoline with the appropriate acid chloride or anhydrid) were subjected to reaction with unsubstituted benzyne (**4a**).



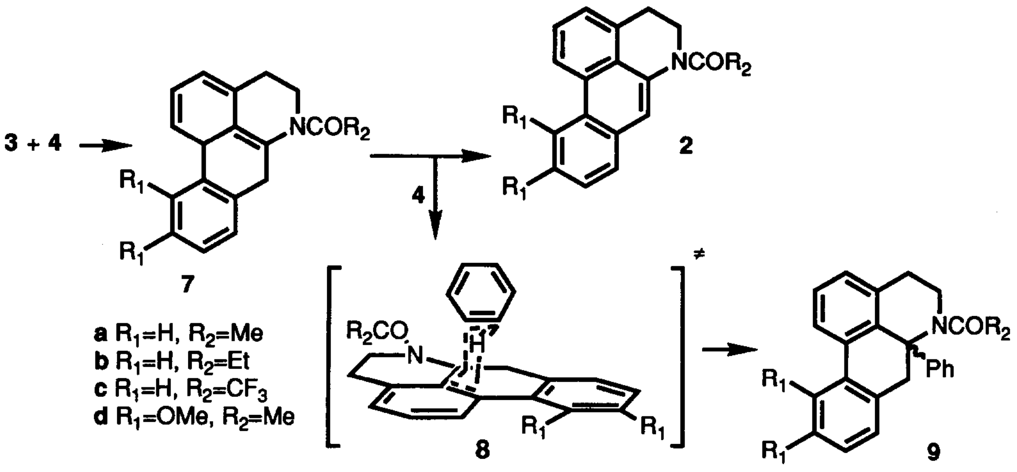
5 **6** **4**

a R_1=H; **b** R_1=OMe

Scheme 2

Treatment of a refluxing solution of **3a** in dimethoxyethane (DME) with benzyne (**4a**) generated by Friedman's method[6] (**Caution! Explosion Hazard**; see Experimental for handling), yielded the desired phenanthrene **2a** in 48 % yield, thus proving that the IBC approach also works well for ring A unsubstituted 1,2,3,4-tetrahydro-1-methyleneisoquinolines. The transformation of the initial adduct **7a** into the observed phenanthrene **2a** involves a dehydrogenation step whose mechanism has been discussed elsewhere [7](Scheme 3).

Reaction of **3b** with benzyne (**4a**) afforded a major compound whose spectroscopic data were in keeping with structure **2b** (26% yield), together with a minor one for which structure **9b** is tentatively proposed. Its molecular ion peak at m/z 353 suggests that two benzyne molecules entered the reaction with the starting diene **3b**. Furthermore, the ^1H NMR spectrum, which exhibits two doublets at 3.49 and 4.90 ppm with a large coupling constant (J=15.7 Hz) together with complicated multiplets due to methylene protons, suggests an aporphinoid skeleton with a phenyl group at C6a. We hypothesize that **9b** may come about by the primary 4 + 2 cycloadduct **7b** undergoing a benzyne promoted ene reaction[8] through transition state **8b** (Scheme 3).



Scheme 3

Similarly, reaction of **3c** with benzyne afforded a major compound whose spectroscopic data were in keeping with structure **2c** (14% yield), together with a minor one for which structure **9c** is tentatively proposed.

In keeping with the above results, reaction of a refluxing DME solution of diene **3a** with asymmetrically substituted 3,4-dimethoxybenzyne (**4b**), provided the expected **2d** regioselectively in 34% isolated yield, the other regioisomer not even being detected in the reaction mixture (^{1}H NMR).[9] For this reaction, **4b** was generated now by thermal decomposition of 3,4-dimethoxybenzenediazonium 2-carboxylate **6b**[10], in turn derived from diazotization of anthranilic acid **5b**[10] (Scheme 2).

Transformation of **2d** into (±)-apomorphine could presumably be accomplished by well known procedures, namely N-deprotection, reduction of the 6a,7 double bond, N-methylation and cleavage of methyl ethers.

Though the IBC approach is not a high yielding reaction, it is our belief that its convergency and regioselectivity may be of great utility for the rapid, flexible synthesis of many other apomorphine analogues, thus facilitating detailed structure-activity studies.

ACKNOWLEDGEMENTS

Financial support from the DGICYT (Project No PB87-0663-C02-01) is gratefully acknowledged.

EXPERIMENTAL PART

General Procedures. All melting points were determined in a Büchi apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Bruker WM-250 (250 MHz) spectrometer with $CDCl_3$ as solvent (unless otherwise noted) and $SiMe_4$ as internal standard. Infrared spectra were recorded in KBr pellets with a Pye-Unicam 1100 spectrometer. Ultraviolet-visible spectra were run on a Pye-Unicam 1700 instrument. Low resolution mass spectra (LRMS) and high resolution mass spectra (HRMS) were recorded on Kratos MS-25 and Kratos MS 50 spectrometers respectively, both operating at 70 eV. Combustion analyses were performed in a Perkin-Elmer 240B at the Microanalysis Service of the University of Málaga. Solvents were dried using standard procedures.[11]

1,2,3,4-Tetrahydro-1-methylene-2-propionylisoquinoline (3b). Addition of triethylamine (1.5 mL, 10.58 mmol) to a cooled (0°C), stirred solution of 3,4-dihydro-1-methylisoquinoline[5] (1.2 g, 8.27 mmol) in dry chloroform was followed by dropwise addition of propionyl chloride (936 mg, 10.11 mmol), and stirring was continued for 10 min. The cooling bath was then removed and the mixture stirred for 4 h at room temperature. The solution was washed with 5% $NaHCO_3$, the organic phase dried with Na_2SO_4 and the solvent evaporated *in vacuo*. The residue was purified by flash chromatography (silicagel, dichloromethane) to yield 1.099 g (66%) of **3b**, mp 42-44°C (petrol ether). UV (EtOH), λ_{max} : 258, 290, 352, 368 nm. IR (KBr) : 1655 cm^{-1}. ^1H NMR δ: 1.11 (t, J = 7.4 Hz, 3H), 2.53 (c, J = 7.4 Hz, 2H), 2.87 (t, J = 6.0 Hz, 2H), 3.97 (t, J = 6.1 Hz, 2H), 5.08 (s, 1H), 5.73 (s, 1H), 7.11-7.13 (m, 1H), 7.19-7.24 (m, 2H), 7.64 (m, 1H) ppm. LRMS m/z (%): 201 (M+, 30). HRMS: calcd. for $C_{13}H_{15}NO$, 201.11536; found 201.11560.

2-Trifluoroacetyl-1,2,3,4-tetrahydro-1-methyleneisoquinoline (3c). Trifluoroacetic anhydride (1.51 mg, 7.2 mmol) in dry pyridine (4mL) was added dropwise to a stirred solution of 3,4-dihydro-1-methylisoquinoline[5] (850 mg, 6.0 mmol) in the same solvent (8 mL). The mixture was stirred for 3 h at room temperature, was dissolved in CH_2Cl_2 (50mL) and washed with $CuSO_4$ (2 x 50 mL) and water (2 x 50 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporaed *in vacuo* to afford **3c** as a white solid (1.0 g, 69% yield). Mp 55-56°C. UV (EtOH), λ_{max} : 240 nm. IR (KBr) : 1670 cm^{-1}. ^1H NMR δ: 3.02 (t, J = 6.1 Hz, 2H), 4.06 (bs, 2H), 5.37 (bs, 1H), 5.77 (bs, 1H), 7.13-7.16 (m, 1H), 7.22-7.23 (m, 2H), 7.59-7.61 (m, 1H) ppm. LRMS m/z (%) : 241 (M+, 66), 171 (64), 144 (71), 114 (100).

General Procedure for Intermolecular Benzyne Cycloaddition. Excess isoamyl nitrite was added over 1-2 min to an ice-cooled stirred solution of the appropriate anthranilic acid **5** in dry DME containing a catalytic amount of trichloroacetic acid. The ice-bath was removed after 15 min and the mixture turned brown-red as it reached room temperature, after which was stirred for an additional 90 min. The following is the recommended handling procedure: *after dilution with DME, most of the solvent is aspirated by means of a plastic syringe equipped with a Teflon® tubing (instead of the standard metallic needle) and discarded.* **Caution! When dry, benzenediazonium-2-carboxylate detonates violently on being scraped or heated.** *The remaining material is washed several times with DME as above until the washing liquors are neutral and the resulting brownish precipitate is suspended in solvent (DME). Successive portions of this suspension are aspirated into a plastic syringe through a Teflon® tube (instead of* *the standard metallic needle) and added dropwise to a refluxing solution of dienes 3 in DME.* When addition was complete (tlc monitoring), the reaction mixture was refluxed for an additional 10 min and then evaporated *in vacuo*. The residue thus obtained was purified by chromatography (silicagel, dichloromethane).

Preparation of 6-acetyl-6a,7-dehydronoraporphine (2a). A suspension of benzenediazonium 2-carboxylate (**6a**) prepared as above from isoamyl nitrite (2.4 g, 20.51 mmol) and anthranilic acid (**5a**, 1.7 g, 12.4 mmol) was added dropwise as above to a refluxing DME solution of 2-acetyl-1,2,3,4-tetrahydro-1-methyleneisoquinoline (**3a**)[5] (300 mg, 1.604 mmol). When addition was complete, the reaction mixture was further refluxed for 10 min and then evaporated *in vacuo*. The residue was chromatographed (silicagel, dichloromethane) affording 200 mg (48%) of 6-acetyl-6a,7-dehydronoraporphine (**2a**), mp 155-7 °C. UV (EtOH), λ_{max} : 263, 300 nm. IR (film) : 1655 cm^{-1}. ^{1}H NMR δ: 2.36 (s, 3H), 3.26 (t, J = 5.6 Hz, 2H), 4.24 (t, J = 5.7 Hz, 2H), 7.33-7.67 (m, 5H), 7.83-7.87 (m, 1H), 8.58-8.67 (m, 2H) ppm. ^{13}C NMR δ: 23.03, 30.58, 42.02, 119.70, 121.13, 124.59, 122.82, 126.39, 126.50, 126.79, 127.24, 127.77, 128.18, 128.77, 130.95, 131.19, 133.47, 169.93 ppm. LRMS m/z (%) : 261 (M$^+$, 60). HRMS calcd. for $C_{18}H_{15}NO$: 261.11536. Found : 261.11510.

Preparation of 6-Propionyl-6a,7-dehydronoraporphine (2b) and 6-propionyl-6a-phenyl-dehydronoraporphine (9b). Refluxing a solution of 1,2,3,4-tetrahydro-1-methylene-2-propionylisoquinoline (**3b**; 200 mg, 0.99 mmol) and benzenediazonium 2-carboxylate (**6a**), prepared as above from anthranilic acid (**5a**, 1.10 g, 8.03 mmol) and isoamyl nitrite (1.55 g, 13.24 mmol) afforded 2-propionyl-6a,7-dehydronoraporphine (**2b**; 71 mg, 26%) and 6a-phenyl-6-propionylnoraporphine (**9a**; 20 mg, 7%).

2b. UV (EtOH), λ_{max} : 260, 305 nm. IR (film) : 1655 cm^{-1}. ^{1}H NMR δ: 1.18 (t, J= 7.4 Hz, 3H), 2.67 (c, J=7.4 Hz, 2H), 3.24 (t, J=5.8 Hz, 2H), 4.23 (t, J=5.8 Hz, 2H), 7.41-7.43 (m, 2H), 7.54-7.66 (m, 3H), 7.86-7.82 (m, 1H), 8.57-8.66 (m, 2H) ppm. ^{13}C NMR δ: 10.00, 27.80, 29.63, 42.33, 119.75, 121.15, 122.85, 124.79, 126.38, 126.52, 126.76, 127.24, 128.24, 128.81, 131.02, 131.26, 133.64, 173.81 ppm. LRMS m/z (%) : 275 (M$^+$, 39). HRMS calcd. for $C_{19}H_{17}NO$: 275.13101. Found : 275.13080.

9b. Mp 185-6 °C (MeOH). UV (EtOH), λ_{max} : 273 nm. IR (film) : 1655 cm^{-1}. ^{1}H NMR δ: 1.13 (t, J=7.3 Hz, 3H), 2.43 (c, J=7.1 Hz, 2H), 3.11 (t, J=5.6 Hz, 2H), 3.50 (d, J=15.9 Hz, 1H), 3.58-3.65 (m, 2H), 4.90 (d, J=15.4 Hz, 1H), 6.96-6.99 (m, 3H), 7.12-7.38 (m, 7H), 7.55-7.63 (m, 2H) ppm. ^{13}C NMR δ: 9.47, 29.45, 30.41, 38.45, 42.10, 64.76, 123.14, 123.27, 126.39, 127.01, 127.16, 127.45, 127.82, 128.22, 128.84, 133.76, 134.61, 135.59, 136.67, 143.47, 173.35 ppm. LRMS m/z (%) : 353 (M$^+$, 30). HRMS calcd. for $C_{25}H_{23}NO$: 353.17795. Found : 353.17850.

Preparation of 6-trifluoroacetyl-6a,7-dehydronoraporphine (2c) and 6-trifluoroacetyl-6a-phenylnoraporphine (9c). Refluxing a solution of 1,2,3,4-tetrahydro-1-methylene-2-propionylisoquinoline (**3c**; 200 mg, 0.99 mmol) and benzenediazonium 2-carboxylate (**6a**), prepared as above from anthranilic acid (**5a**, 1.10 g, 8.03 mmol) and isoamyl nitrite (1.55 g, 13.24 mmol) afforded 2-propionyl-6a,7-dehydronoraporphine (**2c**; 71 mg, 26%) and 6-trifluoroacetyl-6a-phenylnoraporphine (**9c**; 20 mg, 7%).

2c. Mp. 124-125°C (ether-hexane). UV (EtOH), λ_{max} : 258, 304 nm. IR (KBr) : 1685 cm^{-1}. ^{1}H NMR δ: 3.34-3.38 (m, 2H), 4.21 (bs, 2H), 7.41-7.43 (m, 1H), 7.60-7.69 (m, 3H), 7.87-7.90 (m, 1H), 8.20 (bs, 1H), 8.59-8.65 (m, 2H) ppm. ^{13}C NMR δ: 30.89, 45.04, 117.77, 121.19, 121.59, 122.73, 124.07, 126.39, 126.74, 127.07, 127.40, 129.00, 130.96, 131.15, 131.63 ppm. Anal calcd. for $C_{18}H_{12}NOF_3.1/6H_2O$ (%) C = 67.92; H =3 .90; N = 4.40. Found C = 67.99; H = 3.57; N = 4.05.

9c. Mp. 195-196°C (ether-hexane). UV (EtOH), λ_{max} : 272 nm. IR (film) : 1690 cm^{-1}. ^1H NMR δ: 3.13-3.16 (m, 2H), 3.56 (d, J=15.2Hz, 1H), 3.69-3.71 (m, 2H), 4.80 (d, J=15.2 Hz, 1H), 7.02-7.04 (m, 3H), 7.11-7.22 (m, 6H), 7.33-7.40 (m, 1H), 7.58-7.66 (m, 2H) ppm. ^{13}C NMR δ: 29.90, 38.17, 41.81, 66.75, 116.65, 123.28, 123.51, 127.26, 127.39, 127.61, 127.78, 128.02, 128.39, 128.87, 133.41, 133.53, 134.36, 134.65, 134.77, 141.53, 157.70 ppm. LRMS m/z (%) : 393 (M^+, 38), 267 (100), 265 (44), 252 (43). Anal. calcd. for $C_{24}H_{18}NOF_3.1/4H_2O$ (%) C = 72.44; H = 4.69; N = 3.52. Found C = 72.68; H = 4.43; N = 3.31.

Preparation of 6-acetyl-10,11-dimethoxy-6a,7-dehydronoraporphine (2d). A suspension of diazonium salt **6b**[10], prepared as indicated above from anthranilic acid **5b** (410 mg, 2.08 mmol) and isoamyl nitrite (390 mg, 3.34 mmol) was added to a refluxing solution of 6-acetyl-1-methylene-1,2,3,4-tetrahydroisoquinoline (**3a**[5]; 65 mg, 0.347 mmol) in DME. Standard workup procedure furnished 22 mg (34% yield) of adduct **2d**. Mp 126-8°C. UV (EtOH), λ_{max} : 262, 272 nm. IR (film) : 1630, 1655 cm^{-1}. ^1H NMR δ: 2.31 (s, 3H), 3.25 (t, J = 5.7 Hz, 2H), 3.96 (s, 3H), 4.05 (s, 3H), 4.19 (m, 2H), 7.33-7.45 (m, 3H), 7.58-7.64 (m, 2H), 9.59 (d, J = 8.6 Hz, 1H) ppm. ^{13}C NMR δ: 22.98, 30.98, 41.75, 56.63, 59.78, 113.90, 120.30, 123.33, 124.44, 125.52, 126.36, 126.70, 126.87, 127.17, 130.46, 132.72, 147.35, 151.67, 169.91 ppm. LRMS m/z (%) : 321 (M^+, 35). HRMS calcd. for $C_{20}H_{19}NO_3$: 321.13648. Found : 321.13550. Anal. calcd. for $C_{20}H_{19}NO_3$ (%) C = 74.75; H = 5.96; N = 4.63. Found C = 74.49; H = 5.64; N = 4.37.

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