The Synthesis of 2-Amino-4-aryl-3-ethoxycarbonyl-4*H*-naphtho[1,2-*b*]pyrans Revisited

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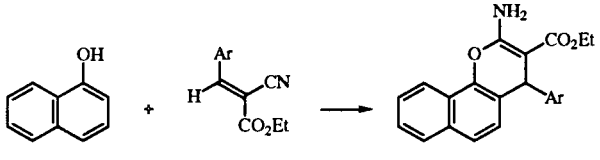
Received February 16, 1995

An expeditious and unequivocal synthesis of some 2-amino-4-aryl-3-ethoxycarbonyl-4*H*-naphtho-[1,2-*b*]pyrans **3** is reported. Previous papers describing the preparation of this type of compound have been amended and a convenient and direct procedure for its preparation is now presented.

J. Heterocyclic Chem., **32**, 1225 (1995).

The biological activity of 2-amino-4-aryl-4*H*-naphtho-[1,2-*b*]pyran-3-carbonitriles **1** [1] has raised a renewed interest for these molecules and analogues [2,3]. Our current and systematic work on the preparation and reactivity of polyfunctionalized 2-amino-4*H*-pyrans [4], has prompted us to synthesize some potential pharmacologically active analogues of **1** as the 2-amino-4-aryl-3-ethoxycarbonyl-4*H*-naphtho[1,2-*b*]pyrans **3** (Scheme). Very surprisingly, after careful revision of the dispersed available literature, we have found that these compounds were not described. Indeed, it has been reported that the condensation of 1-naphthol with arylidenecyanoacetates **2** and piperidine (catalytic) fails (Scheme) [5]. More recently, it has been claimed [6] that the same reaction, but using pyridine as base-solvent, gives the cited products. However, their analytical, physical and spectroscopic data were omitted. Apparently, it could be assumed that these products were already known, but no reference was provided and, in fact, we could not find them in any other report [7].

Scheme



2a-g **3a-g**

With these confusing and contradictory precedents in mind, we have again addressed the problem of the synthesis of 2-amino-4-aryl-3-ethoxycarbonyl-4*H*-naphtho-[1,2-*b*]pyrans and in this paper we report the successful accomplishment of this goal.

We have observed that the previous conclusions [5,6] were erroneous and the following conclusions can be advanced: (1) Using pyridine [6], the condensation of 1-naphthol with arylidenecyanoacetates **2** does not give products **3**, after refluxing for 48 hours. (2) On the contrary, the same reaction under reflux, catalyzed by piperidine, affords the desired 4*H*-naphtho[1,2-*b*]pyrans (Scheme) under mild conditions and in excellent yield (Table 1). When an equimolecular amount of piperidine was used, at refluxing temperature, the reaction was faster but the yield was lower (Table 1). The reaction of 1-naphthol with ethyl α-cyanocinnamate at room temperature was slow (6 hours with equimolecular quantities of piperidine and 72 hours with a catalytic amount of piperidine).

Table 1

Experimental Conditions for the Synthesis of 4*H*-Naphtho[1,2-*b*]pyrans **3a-g**

3	Ar	Piperidine (equivalent)	Time (hours)	Yield (%)
a	C_6H_5	0.2	10	82
		1.0	1	62
b	*p*-CH_3O-C_6H_4	0.2	72	75
		1.0	1	64
c	*p*-NO_2-C_6H_4	0.2	2	88
		1.0	0.75	69
d	*p*-Cl-C_6H_4	0.2	4	84
		1.0	0.75	65
e	*p*-CH_3-C_6H_4	0.2	16	77
		1.0	1	54
f	*p*-CN-C_6H_4	0.2	3	80
		1.0	0.75	68
g	3,4-$(CH_3O)_2C_6H_3$	0.2	72	70
		1.0	3	55

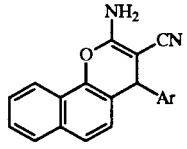


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Figure 1

Compounds **3** were isolated as stable, pale yellow solids. They showed excellent analytical and spectroscopic data (see Experimental). In the ir spectra, the bands at 3440-3380 and 3310-3280 cm^{-1} are attributed to the ν (N-H) vibration. The band at 1680-1665 cm^{-1} is assigned to ν (C=O) vibration of the chelated carbonyl group. The two remaining bands which appear in the double bond region at 1620-1600 and 1530-1520 cm^{-1} are considered to arise from skeletal vibrations of the enamino group and are consequently assigned to mixed vibrations with contributions of ν (C=C), ν (C-N) and δ (NH_2) modes. In the ^1H nmr spectra, characteristic signals for H-4 appear as singlets, at 5.18-4.99 ppm. In the ^{13}C nmr spectra (Table 2) we could unequivocally assign the signals on the basis of the observed chemical shifts and by comparison with the known and standard chemical shifts for 2-amino-4*H*-pyrans [8], on DEPT experiments and also on the signal multiplicities and the long-range J values obtained from the proton-coupled spectra. All these values strongly confirm the structure of our molecules and support the validity of the present method for their preparation.

Table 2

Selected ^{13}C Chemical Shifts (ppm) of 4*H*-Naphtho[1,2-*b*]pyrans **3a-g**

3	C-2	C-3	C-4	C-4a	C-6a	C10-a	C-10b
a	160.0	78.7	40.9	120.8	133.0	123.4	143.2
b	159.9	79.4	40.0	121.0	132.9	123.4	143.1
c	160.1	77.9	40.9	118.9	133.2	123.3	143.3
d	159.9	78.7	40.3	120.1	133.0	123.3	143.1
e	160.0	79.3	40.4	121.0	132.9	123.4	143.2
f	160.1	78.0	41.1	119.1 [a]	133.2	124.4	143.5
g	160.0	79.3	40.5	120.9	132.9	123.4	143.1

[a] This peak could be exchanged with the signal at 119.1 ppm.

In summary, we have characterized and described the interesting and complex 2-amino-4-aryl-3-ethoxycarbonyl-4*H*-naphtho[1,2-*b*]pyrans **3**, correcting some previous confusing and erroneous reports. The synthetic protocol proceeds under mild conditions and gives these products in high yield. Application of this methodology to other substrates is under current research in our laboratory and will be reported in due course.

EXPERIMENTAL

All the reactions were monitored by tlc using precoated silica gel aluminium plates containing a fluorescent indicator (Merck, 5539). Detection was by uv (254 nm). Flash column chromatography [9] was performed using Kieselgel 60 (230-400 mesh, Merck) and hexane-ethyl acetate mixtures as the eluent. Melting points were determined in capillary tubes and are uncorrected. The ir spectra were recorded with a Perkin-Elmer 681 spectrometer as potassium bromide pellets. The ^1H nmr spectra were recorded on a Varian XL-300 spectrometer. The ^{13}C nmr spectra were recorded on a Bruker AM-200 (50 MHz). Elemental analyses were obtained in the Microanalysis Service of the IQOG (CSIC).

General Procedure for the Synthesis of 2-Amino-4-aryl-3-ethoxycarbonyl-4*H*-naphtho[1,2-*b*]pyrans **3**.

To a stirred mixture of 1-naphthol (5.0 mmoles, 1.0 equivalent) and the corresponding α-cyanocinnamate **2a-g** (5.0 mmoles, 1.0 equivalents) in ethanol (15 ml), piperidine (1.0 mmole, 0.2 equivalent) was added. The mixture was refluxed for the length of time indicated in Table 1. The yellow-orange solution was cooled to room temperature and the solvent evaporated. The crude material was submitted to flash chromatography (hexane/ethyl acetate, 9:1) yielding compounds **3** as light yellow solids.

2-Amino-3-ethoxycarbonyl-4-phenyl-4*H*-naphtho[1,2-*b*]pyran (**3a**).

Following the general procedure, using ethyl α-cyanocinnamate **2a**, after 10 hours, compound **3a** (1.41 g, yield 82%) was obtained, mp 147-149°; ir: ν 3390, 3280, 2980, 1665, 1640, 1600, 1520, 1505, 1470, 1450, 1410, 1380, 1310, 1270, 1090 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.23 (d, 1H, J = 8.4 Hz, aromatic), 7.76 (d, 1H, J = 8.7 Hz, aromatic), 7.60-7.43 (m, 3H, aromatic), 7.30-7.10 (m, 6H, aromatic), 6.47 (br s, 2H, NH_2), 5.08 (s, 1H, H-4), 4.10 (q, 2H, OCH_2CH_3), 1.19 (t, 3H, OCH_2CH_3); ^{13}C nmr (deuteriochloroform): δ 169.5 (CO_2Et), 160.0 (C-2), 147.6 (C_{ipso}), 143.2 (C-10b), 133.0 (C-6a), 128.1, 128.0, 127.6, 126.7, 126.2, 126.2, 126.1, 124.0, 120.8 (aromatic), 123.4 (C-10a), 120.8 (C-4a), 78.7 (C-3), 59.4 (CH_2), 40.9 (C-4), 14.3 (CH_3); ms: m/z 345 (M^+, 13), 316 (4), 298 (5), 272 (13), 268 (100), 240 (12), 222 (35), 194 (7), 166 (5), 139 (7), 115 (3), 77 (4).

Anal. Calcd. for $C_{22}H_{19}NO_3$ (345.40): C, 76.50; H, 5.54; N, 4.05. Found: C, 76.26; H, 5.80; N, 4.13.

2-Amino-3-ethoxycarbonyl-4-(*p*-methoxyphenyl)-4*H*-naphtho-[1,2-*b*]pyran (**3b**).

Following the general procedure, using ethyl α-cyano(*p*-methoxy)cinnamate **2b**, after 72 hours, compound **3b** (1.124 g, yield 75%) was obtained, mp 152-154°; ir: ν 3390, 3280, 2980, 1670, 1640, 1610, 1530, 1510, 1470, 1400, 1380, 1300, 1270, 1230, 1090 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.22 (d, 1H, J = 8.4 Hz, aromatic), 7.76 (d, 1H, J = 7.8 Hz, aromatic), 7.58-7.45 (m, 3H, aromatic), 7.25-7.15 (m, 3H, aromatic), 6.78 (m, 2H, aromatic), 6.47 (br s, 2H, NH_2), 5.04 (s, 1H, H-4), 4.15 (q, 2H, OCH_2CH_3), 3.74 (s, 3H, OCH_3), 1.23 (t, 3H, OCH_2CH_3); ^{13}C nmr (deuteriochloroform): δ 169.5 (CO_2Et), 159.9 (C-2), 143.1 (C-10b), 132.9 (C-6a), 157.9, 140.0, 129.0, 127.6, 126.7, 126.4, 126.2, 124.0, 120.8, 113.5 (aromatic), 123.4 (C-10a), 121.0 (C-4a), 79.4 (C-3), 59.4 (CH_2), 55.1 (OCH_3), 40.0 (C-4), 14.3 (CH_3); ms: m/z 375 (M^+, 9), 328 (6), 302 (12), 268 (100), 240 (12), 222 (46), 194 (9), 166 (11), 139 (15), 115 (8).

Anal. Calcd. for $C_{23}H_{21}NO_4$ (375.42): C, 73.58; H, 5.64; N, 3.73. Found: C, 73.38; H, 5.38; N, 3.52.

2-Amino-3-ethoxycarbonyl-4-(*p*-nitrophenyl)-4*H*-naphtho-[1,2-*b*]pyran (**3c**).

Following the general procedure, using ethyl α-cyano-*p*-nitrocinnamate **2c**, after 2 hours, compound **3c** (1.715 g, yield 88%)

was obtained as an oil; ir (film): ν 3440, 3310, 2980, 1680, 1650, 1620, 1520, 1470, 1400, 1380, 1350, 1310, 1270, 1090 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.23 (d, 1H, J = 8.4 Hz, aromatic), 8.11-8.07 (m, 2H, aromatic), 7.78 (d, 1H, J = 8.7 Hz, aromatic), 7.60-7.42 (m, 5H, aromatic), 7.07 (d, 1H, J = 8.4, aromatic), 6.58 (br s, 2H, NH_2), 5.18 (s, 1H, H-4), 4.11 (q, 2H, OCH_2CH_3), 1.18 (t, 3H, OCH_2CH_3); ^{13}C nmr (deuteriochloroform): δ 168.9 (CO_2Et), 160.1 (C-2), 143.3 (C-10b), 133.2 (C-6a), 154.9, 146.4, 128.8, 127.7, 126.7, 126.6, 126.0, 124.5, 123.6, 120.8 (aromatic), 123.3 (C-10a), 118.9 (C-4a), 77.9 (C-3), 59.7 (CH_2), 40.9 (C-4), 14.3 (CH_3); ms: m/z 390 (M^+, 11), 317 (15), 268 (88), 222 (43), 88 (30), 86 (72), 84 (100), 49 (43).

Anal. Calcd. for $C_{22}H_{18}N_2O_5$ (390.40): C, 67.68; H, 4.65; N, 7.17. Found: C, 67.89; H, 4.45; N, 6.98.

2-Amino-4-(*p*-chlorophenyl)-3-ethoxycarbonyl-4*H*-naphtho-[1,2-*b*]pyran (**3d**).

Following the general procedure, using ethyl α-cyano-*p*-chlorocinnamate **2d**, after 4 hours, compound **3d** (1.60 g, yield 84%) was obtained, mp 127-129°; ir: ν 3390, 3290, 2980, 1670, 1645, 1610, 1525, 1505, 1490, 1480, 1400, 1380, 1310, 1270, 1230, 1090 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.22 (d, 1H, J = 8.4 Hz, aromatic), 7.76 (d, 1H, J = 8.4 Hz, aromatic), 7.60-7.47 (m, 3H, aromatic), 7.25-7.18 (m, 4H, aromatic), 6.78 (m, 1H, aromatic), 6.50 (br s, 2H, NH_2), 5.05 (s, 1H, H-4), 4.11 (q, 2H, OCH_2CH_3), 1.20 (t, 3H, OCH_2CH_3); ^{13}C nmr (deuteriochloroform): δ 169.3 (CO_2Et), 159.9 (C-2), 143.1 (C-10b), 133.0 (C-6a), 146.1, 131.8, 129.3, 128.2, 127.7, 126.4, 126.4, 124.2, 120.8 (aromatic), 123.3 (C-10a), 120.1 (C-4a), 78.7 (C-3), 59.6 (CH_2), 40.3 (C-4), 14.3 (CH_3); ms: m/z 379 (M^+, 10), 350 (5), 306 (13), 268 (100), 240 (11), 222 (37), 194 (5), 166 (6), 139 (7), 115 (2).

Anal. Calcd. for $C_{22}H_{18}ClNO_3$ (379.84): C, 69.56; H, 4.77; N, 3.69. Found: C, 69.57; H, 5.03; N, 3.70.

2-Amino-3-ethoxycarbonyl-4-(*p*-methylphenyl)-4*H*-naphtho-[1,2-*b*]pyran (**3e**).

Following the general procedure, using ethyl α-cyano-*p*-methylcinnamate **2e**, after 16 hours, compound **3e** (1.385 g, yield 77%) was obtained, mp 110-112°; ir: ν 3380, 3300, 2980, 1670, 1645, 1610, 1520, 1505, 1400, 1380, 1310, 1270, 1230, 1090 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.23 (d, 1H, J = 8.4 Hz, aromatic), 7.76 (d, 1H, J = 8.4 Hz, aromatic), 7.58-7.46 (m, 3H, aromatic), 7.20 (m, 3H, aromatic), 7.04 (m, 2H, aromatic), 6.45 (br s, 2H, NH_2), 5.05 (s, 1H, H-4), 4.12 (q, 2H, OCH_2CH_3), 2.27 (s, 3H, CH_3), 1.23 (t, 3H, OCH_2CH_3); ^{13}C nmr (deuteriochloroform): δ 169.5 (CO_2Et), 160.0 (C-2), 143.2 (C-10b), 132.9 (C-6a), 144.6, 135.6, 128.8, 127.8, 127.6, 126.7, 126.2, 126.1, 124.0, 120.8 (aromatic), 123.4 (C-10a), 121.0 (C-4a), 79.3 (C-3), 59.5 (CH_2), 40.4 (C-4), 21.0 (CH_3), 14.3 (OCH_2CH_3); ms: m/z 359 (M^+, 11), 330 (4), 312 (5), 286 (16), 268 (100), 240 (8), 222 (33), 178 (11), 144 (47), 115 (57), 91 (66), 65 (12), 43 (12).

Anal. Calcd. for $C_{23}H_{21}NO_3$ (359.42): C, 76.86; H, 5.89; N, 3.89. Found: C, 77.00; H, 6.00; N, 3.70.

2-Amino-4-(*p*-cyanophenyl)-3-ethoxycarbonyl-4*H*-naphtho-[1,2-*b*]pyran (**3f**).

Following the general procedure, using ethyl α-cyano-*p*-cyanocinnamate **2f**, after 3 hours, compound **3f** (1.48 g, yield 80%) was obtained, mp 133-135°; ir (film): ν 3420, 3310, 3060, 2980, 2230, 1680, 1650, 1610, 1525, 1505, 1470, 1400, 1380, 1310, 1270, 1230, 1090 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.23 (d, 1H, J = 8.4 Hz, aromatic), 7.78 (d, 1H, J = 8.4 Hz, aromatic), 7.60-7.48 (m, 5H, aromatic), 7.41-7.36 (m, 2H, aromatic), 7.07 (d, 1H, J = 8.4 Hz, aromatic), 6.56 (br s, 2H, NH_2), 5.12 (s, 1H, H-4), 4.11 (q, 2H, OCH_2CH_3), 1.17 (t, 3H, OCH_2CH_3); ^{13}C nmr (deuteriochloroform): δ 169.3 (CO_2Et), 160.1 (C-2), 143.5 (C-10b), 133.2 (C-6a), 152.9, 132.1, 128.8, 127.7, 126.6, 126.6, 126.1, 120.8, 110.0 (aromatic), 124.4 (C-10a), 119.1, 119.1 (C-4a and CN), 78.0 (C-3), 59.6 (CH_2), 41.1 (C-4), 14.3 (CH_3); ms: m/z 370 (M^+, 11), 341 (6), 297 (18), 268 (100), 240 (13), 222 (38), 194 (5), 166 (6), 139 (8), 115 (3).

Anal. Calcd. for $C_{23}H_{18}N_2O_3$ (370.41): C, 74.58; H, 4.90; N, 7.56. Found: C, 74.64; H, 4.97; N, 7.22.

2-Amino-3-ethoxycarbonyl-4-(3,4-dimethoxyphenyl)-4*H*-naphtho[1,2-*b*]pyran (**3g**).

Following the general procedure, using ethyl α-cyano-3,4-dimethoxycinnamate **2g**, after 72 hours, compound **3g** (1.415 g, yield 70%) is obtained, mp 134-136°; ir (film): ν 3420, 3310, 3060, 2980, 1680, 1620, 1520, 1470, 1400, 1380, 1310, 1270, 1230, 1180, 1090 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.21 (d, 1H, J = 8.4 Hz, aromatic), 7.76 (m, 1H, aromatic), 7.55-7.43 (m, 3H, aromatic), 7.16 (d, 1H, J = 8.4 Hz, aromatic), 6.82-6.69 (m, 3H, aromatic), 6.50 (br s, 2H, NH_2), 4.99 (s, 1H, H-4), 4.09 (q, 2H, OCH_2CH_3), 3.80 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 1.20 (t, 3H, OCH_2CH_3); ^{13}C nmr (deuteriochloroform): δ 169.5 (CO_2Et), 160.0 (C-2), 143.1 (C-10b), 132.9 (C-6a), 148.6, 147.4, 140.5, 127.6, 126.6, 126.2, 126.1, 124.0, 120.8, 120.0, 111.4, 111.1 (aromatic), 123.4 (C-10a), 120.9 (C-4a), 79.3 (C-3), 59.4 (CH_2), 55.8 (2 OCH_3), 40.5 (C-4), 14.4 (CH_3), ms m/z: 405 (M^+, 9), 376 (17), 358 (9), 268 (100), 240 (8), 222 (34), 194 (4), 166 (4), 139 (4).

Anal. Calcd. for $C_{24}H_{23}NO_5$ (405.45): C, 71.09; H, 5.72; N, 3.45. Found: C, 70.98; H, 6.00; N, 3.29.

Acknowledgments.

The authors thank DGICYT (PB 90-0078 and PB 92-0237) for financial support and Mrs. Mercedes Plaza (IQOG, CSIC) for recording the ^1H and ^{13}C nmr spectra. A.M.-G. also thanks U. Complutense of Madrid for a research fellowship.

REFERENCES AND NOTES

[1] M. Brunavs, C. P. Dell, P. T. Gallagher, W. M. Owton, and C. W. Smith, European Patent Appl. EP 557,075; *Chem. Abstr.*, **120**, 106768t (1994).

[2] J. Bloxham, C. P. Dell, and C. W. Smith, *Heterocycles*, **38**, 399 (1994).

[3] A. G. A. Elagamey and F. M. A. El-Taweel, *Indian J. Chem.*, **29B**, 885 (1990).

[4] N. Martín, A. Martínez-Grau, C. Seoane, J. L. Marco, A. Albert, and F. H. Cano, *Liebigs Ann. Chem.*, 801 (1993), and references cited therein.

[5] A. G. A. Elagamey, S. Z. Sawllim, F. M. A. El-Taweel, and M. H. Elnagdi, *Collect. Czech. Chem. Commun.*, **53**, 1534 (1988).

[6] M. H. Elnagdi, A. H. H. Elghandour, M. K. A. Ibrahim, and I. S. A. Hafiz, Z. *Naturforsch.*, **47b**, 572 (1992).

[7] Other different 4-aryl substituted 3-alkoxycarbonyl-2-amino-4*H*-naphtho[1,2-*b*]pyrans have been prepared in two recent patents, in

which no spectroscopic or analytical data were provided: [a] C. P. Dell and C. W. Smith, European Patent Appl. EP 537,949; *Chem. Abstr.*, **119**, 139102d (1993); [b] C. P. Dell and C. W. Smith, US Patent 5,281,619; *Chem. Abstr.*, **120**, 208603c (1994).

[8] C. Pascual, N. Martín, and C. Seoane, *Magn. Reson. Chem.*, **23**, 793 (1985).

[9] W. C. Still, M. Khan, and A. Mitra, *J. Org. Chem.*, **23**, 2923 (1978).