A Convenient One-Pot Synthesis of 2,2-Dialkyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans

Amitabh Jha,* Po-Jung Jimmy Huang, Chandrani Mukherjee, Nawal K. Paul

Department of Chemistry, Acadia University, Wolfville, NS, B4P 2R6, Canada
Fax +1(902)5851114; E-mail: ajha@acadiau.ca

Received 28 August 2007

Abstract: This work describes a convenient one-pot procedure for the synthesis of 2,2-disubstituted 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans {i.e. 2,2-disubstituted 1*H*-benzo[*f*]chromans} by the reaction of 2-tetralones and α,α-disubstituted β-hydroxy propionaldehydes under acidic conditions.

Key words: naphthopyran, aromatization, cyclizations, fused-ring systems, alkylation, rearrangements

Naphtho[2,1-*b*]pyrans, also known as 1*H*-benzo[*f*]chromenes, are well known for their photochromic properties.[1] This property is the result of a facile electrocyclic pyran ring opening to yield a mixture of yellow- or purple-colored geometrical isomers that gradually cyclize back to the colorless pyran ring upon removal of the source of irradiation:[1] leading to their importance in photochromic lenses which darken upon exposure to sunlight.[2] Furthermore, naphthopyrans are prevalent in numerous natural products with significant biological and medicinal properties.[3] Hence, the syntheses of naphthopyrans are of importance as they are of value for a variety of applications.

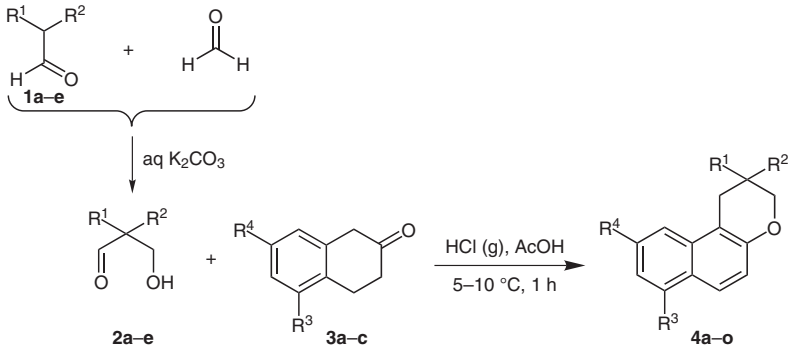
Several synthetic approaches to naphthopyrans have been described but they generally lack simplicity and satisfactory yields. Some methodologies for preparing naphthopyrans with photochromic properties[4] involve multistep strategies initiating from chromanones[4a] or via Grignard reactions on benzocoumarins followed by dehydration.[4b] Other methods involve the Claisen rearrangement of propargyl aryl ethers obtained in situ from reaction of α,α-disubstituted propargyl alcohols with phenols under acidic conditions.[4c–g] In some reports, catalysts like pyridinium *p*-toluenesulfonate have been employed to improve the yield.[4]

Numerous related procedures are known for the synthesis of the 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran analogues with a saturated pyran ring {1*H*-benzo[*f*]chromans} which are devoid of photochromic behavior.[5] 2,3-Dihydro-1*H*-naphtho[2,1-*b*]pyran was prepared in 31% yield by heating 2-allyloxy-1-bromonaphthalene and AIBN in benzene using a modified stannane reagent;[5a] the conventional reagent Bu_3SnH gave only ca. 17% yield.[5b] When 1-bromo-2-but-3-enyloxy-naphthalene was used as starting material, 2-methyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran was obtained as one of the products.[5c] A similar example starting from 2-allyloxy-1-iodonaphthalene involved use of 9-BBN and palladium-catalyzed intramolecular cross-coupling reaction.[5d] Another related reaction on 2-allyloxy-1-iodonaphthalene using phosphinic acid, AIBN, and $NaHCO_3$ is also known.[5e,f] Photoexcitation of 1-allyl-2-naphthols resulted in formation of 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran in 13% yield among several byproducts.[5g] 2,3-Dihydro-1*H*-naphtho[2,1-*b*]pyran was also obtained from 1-(3-hydroxypropyl)naphthalen-2-ol by intramolecular cyclization in low yields.[5h,i] A multistep synthesis of 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran from 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran-1-one following a reduction, dehydration, and hydrogenation sequence is also known.[5j] In an electron-transfer reaction, methylene blue catalyzed photodecarboxylation of 1-allyl-2-naphthoxy acetic acid led to formation of 2-methyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran in 55% yield.[5k,l] Impressive results were reported by Sih and He[5m] who synthesized 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran in 90% yield by expensive Au(III)-catalyzed C–C bond formation of 2-naphthyloxypropyl triflate or methane sulfonate ester. In a related endeavor, the same group reported Au(III)-catalyzed intramolecular cycloalkylation of 2-(2-naphthyloxymethyl)oxirane to 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran-1-ol in 89% yield.[5n] All these procedures suffer from drawbacks such as multiple step syntheses, poor yields, significant amounts of byproducts, and/or use of expensive reagents.

It is quite clear from the above discussion that simple and cost-effective synthesis of 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran-type compounds has thus far proved elusive. We report herein a convenient and one-pot synthesis of 2,3-dihydro-1*H*-naphtho[*2,1-b*]pyrans **4a–o** starting from α,α-disubstituted β-hydroxy propionaldehydes **2a–e** and commercially available 2-tetralones **3a–c** (Scheme 1).

We have previously reported the synthesis of 2-alkoxy-1-arylmethylnaphthalenes from 2-tetralone, aldehydes, and alcohols under acidic conditions.[6] The most plausible mechanism of formation involves mixed aldol condensation of the most active methylene of 2-tetralone with aldehyde, then vinyl ether formation followed by rearrangement to produce the more stable species through aromatization. Subsequently, 12*H*-benzo[*a*]xanthenes were prepared from 2-tetralone and substituted *ortho*-hydroxy aromatic aldehydes in a related endeavor.[7]

SYNLETT 2007, No. 20, pp 3127–3130
Advanced online publication: 21.11.2007
DOI: 10.1055/s-2007-992380; Art ID: S06507ST



Scheme 1 Synthetic scheme for preparing 1*H*-benzo[*f*]chromenes **4a–o**. Refer to Table 1 for R^1–R^4 substituents.

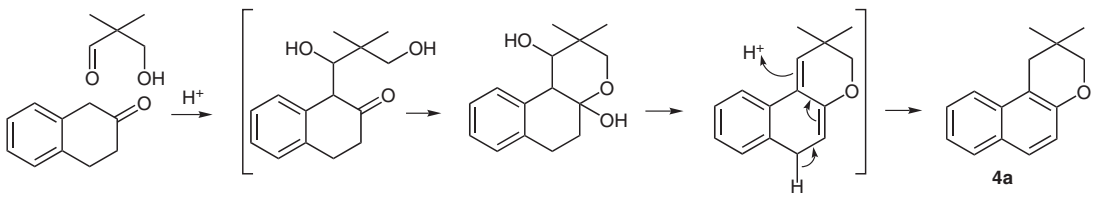
The present work constitutes an extension of our previous results describing the synthesis of 12*H*-benzo[*a*]xanthenes.[7] It was proposed that the aldehyde-active methylene condensation led to (*E*)-1-arylidene-2-tetralones[8] as intermediates where the position of the hydroxyl group was such that concomitant cyclization was unlikely; the presence of the extended conjugation from the hydroxyl group to carbonyl function made the conversion of *E*-isomer to *Z*-isomer possible and therefore cyclization ensued.[7] We decided to react 2-tetralone and β-hydroxy aliphatic aldehydes under similar conditions to confirm if the presence of the extended conjugation is an absolute requirement.

The synthesis involves anhydrous conditions using dry HCl gas in acetic acid (Scheme 1). The necessary α,α-disubstituted β-hydroxy propionaldehydes **2a–e** were obtained by simple base-promoted mixed aldol condensations of appropriately substituted aliphatic aldehydes **1a–e** and formalin following literature procedures.[9] All the final compounds (**4a–o**, Scheme 1) are new to chemical literature and completely characterized by spectroscopic data.[10] Table 1 reports the yields, melting points, and HRMS data of the final naphthopyran products where appropriate.

It is documented (X-ray crystallographic studies) that the reaction of 2-tetralone with one equivalent of aromatic aldehydes under suitable conditions exclusively produce 1-arylidene-2-tetralones with more stable *E*-geometry.[8] Only the *Z*-isomer of the intermediate 1-alkylidene-2-tetralone can cyclize to the corresponding naphtho[2,1-*b*]pyrans. When α,α-disubstituted β-hydroxy propionaldehydes **2a–e** were reacted with 2-tetralone or its analogues **3a–c**, naphtho[2,1-*b*]pyrans **4a–o** were the only products isolated in satisfactory to good yields (Table 1). This result implies that extended conjugation, as we previously suggested,[7] may not be the sole factor in facilitating cyclization.

After close examination, three possibilities were noted by which this cyclization may have resulted. Either a self-assembly (due to H-bonding) or reversible addition–elimination of HCl across the newly created *E* double bond leads to the formation of the *Z*-isomer of the 1-alkylidene-2-tetralone intermediate. The hydroxyl and carbonyl functional groups in the resulting *Z*-enone are in excellent proximity and orientation for the cyclization to occur via nucleophilic attack, followed by dehydration and rearrangement. Alternatively, the aldol initially formed cyclizes to a hemiacetal which undergoes double dehydration and rearrangement leading to the formation of aromatic naphtho[2,1-*b*]pyrans **4a–o** (Scheme 2). This appears to be the most reasonable possibility as it eliminates the geometrical prerequisites for intermediate enones (vide supra) to cyclize.

Another puzzling aspect of this chemistry involves the use of primary alcohols with a quaternary β-position. These substrates are well known to undergo facile rearrangement involving 1,2-alkyl shift, leading to tertiary carbocation under acidic conditions.[11] It was therefore expected that the formation of conjugated tertiary carbocations in present scenario would eventually lead to naphthofuran derivatives. However, this was not observed. Solvent polarity plays an important role in reactions involving carbocation intermediates – use of acetic acid (ε = 6) as a solvent is not most conducive; more polar solvents such as formic acid (ε = 58) and water (ε = 78) lead to faster reaction rates.[12] This prompted us to replicate the reactions of 2,2-dimethyl-3-hydroxypropanal (**2a**) with 2-tetralone in anhydrous formic acid[13] as well as in 50% aqueous formic



Scheme 2 Most plausible mechanism of formation of representative 2,3-dihydro-2,2-dimethyl-1*H*-benzo[*f*]chromene (**4a**) from 2-tetralone and 3-hydroxy-2,2-dimethylpropanal.

Table 1 Physical Data of Compounds **4a–o**

Compd	R^1	R^2	R^3	R^4	mp (°C)	HRMS Calcd	HRMS Found	Yield (%)[a]
4a	Me	Me	H	H	96-98	212.1201	212.1193	70[b]
4b	Me	Me	OMe	H	–	242.1307	242.1302	61
4c	Me	Me	H	OMe	–	242.1307	242.1291	58
4d	Et	Et	H	H	–	240.1514	240.1530	79
4e	Et	Et	OMe	H	93–95	270.1620	270.1633	51
4f	Et	Et	H	OMe	61–63	270.1620	270.1610	63
4g	$-(CH_2)_5-$		H	H	96–98	252.1514	252.1508	75
4h	$-(CH_2)_5-$		OMe	H	91–93	282.1620	282.1623	50
4i	$-(CH_2)_5-$		H	OMe	130–132	282.1620	282.1624	62
4j	Et	*n*-Bu	H	H	–	268.1827	268.1815	75
4k	Et	*n*-Bu	OMe	H	–	298.1933	298.1931	63
4l	Et	*n*-Bu	H	OMe	–	298.1933	298.1935	58
4m	Me	Ph	H	H	102–104	274.1358	274.1352	70
4n	Me	Ph	OMe	H	88–91	304.1463	304.1480	59
4o	Me	Ph	H	OMe	102–105	304.1463	304.1472	63

[a] Isolated yields.
[b] Compound **1** was obtained in 96.4% and 89.6% isolated yields when reaction was performed in anhyd formic acid and 50% aq formic acid, respectively.

acid. Both reactions yielded compound **1** as the only product in significantly higher yields (Table 1, footnote b) and there was no trace of any naphthofuran product. Upon retrospection it was discerned that the prospective carbocation would be destabilized by the vicinal carbonyl functionality preventing this mechanistic possibility.

In conclusion, we have successfully synthesized fifteen new 2,3-dihydronaphtho[2,1-*b*]pyrans from 2-tetralone analogues and α,α-disubstituted β-hydroxy propionaldehydes. The synthetic methodology involves facile acid-catalyzed aldol condensation, cyclization, and aromatization sequence. This procedure is completely unrelated to any known procedure for the preparation of 2,3-dihydronaphtho[2,1-*b*]pyrans. Following a similar protocol, the synthesis of optically pure novel glyconaphthopyrans is under investigation using 2-tetralone analogues and β-hydroxyaldehydes obtained from sugars.

Acknowledgment

The authors thank the Natural Sciences and Engineering Research Council of Canada and Acadia University for financial support for this project. Mr. Arun Sehgal of Chempro Exports (India) is thanked for providing the complimentary samples of 5-methoxy-2-tetralone and 7-methoxy-2-tetralone.

References and Notes

(1) (a) Nakatsuji, S. *Chem. Soc. Rev.* **2004**, *33*, 348. (b) Gabbutt, C. D.; Hepworth, J. D.; Heron, B. M.; Thomas, D. A.; Kilner, C.; Partington, S. A. *Heterocycles* **2004**, *63*, 567. (c) Jockusch, S.; Turro, N. J.; Blackburn, F. R. *J. Phys. Chem. A* **2002**, *106*, 9236.
(2) Van Gemert, B. *Mol. Cryst. Liq. Cryst.* **2000**, *344*, 57.
(3) (a) Hollick, J. J.; Golding, B. T.; Hardcastle, I. R.; Martin, N.; Richardson, C.; Rigoreau, L. J. M.; Smith, G. C. M.; Griffin, R. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3083. (b) Hussein, A. A.; Barberena, I.; Capson, T. L.; Kursar, T. A.; Coley, P. D.; Solis, P. N.; Gupta, M. P. *J. Nat. Prod.* **2004**, *67*, 451. (c) Moharram, S.; Zhou, A.; Wiebe, L. I.; Knaus, E. E. *J. Med. Chem.* **2004**, *47*, 1840. (d) Visentin, S.; Rolando, B.; Di Stilo, A.; Fruttero, R.; Novara, M.; Carbone, E.; Roussel, C.; Vanthuyne, N.; Gasco, A. *J. Med. Chem.* **2004**, *47*, 2688. (e) Wood, D. L.; Panda, D.; Wiernicki, T. R.; Wilson, L.; Jordan, M. A.; Singh, J. P. *Mol. Pharmacol.* **1997**, *52*, 437.
(4) (a) Gabbutt, C. D.; Hartley, D. J.; Hepworth, J. D.; Heron, B. M.; Kanjia, M.; Rahman, M. *Tetrahedron* **1994**, *50*, 2507. (b) Cottam, J.; Livingstone, R. *J. Chem. Soc.* **1965**, 6646. (c) Momoda, J.; Hara, T. US 5808100, **1998**. (d) Tanaka, K.; Aoki, H.; Hosomi, H.; Ohba, S. *Org. Lett.* **2000**, *2*, 2133. (e) Coelho, P. J.; Carvalho, L. M.; Abrantes, S.; Oliveira, M. M.; Oliveira-Campos, A. M. F.; Dubest, R.; Samat, A.; Guglielmetti, R. *Tetrahedron* **2002**, *58*, 9505. (f) Harie, G.; Samat, A.; Guglielmetti, R. *Tetrahedron Lett.* **1997**, *38*, 3075. (g) Pozzo, J. L.; Samat, A.; Guglielmetti, R.; Lokshin, V.; Minkin, V. *Can. J. Chem.* **1996**, *74*, 1649. (h) Zhao, W.; Carreira, E. M. *Org. Lett.* **2003**, *5*, 4153.

(5) (a) Clive, D. L. J.; Wang, J. *J. Org. Chem.* **2002**, *67*, 1192. (b) Abeywickrema, A. N.; Beckwith, A. L. J.; Gerba, S. *J. Org. Chem.* **1987**, *52*, 4072. (c) Branchi, B.; Galli, C.; Gentili, P. *Eur. J. Org. Chem.* **2002**, 2844. (d) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314. (e) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 225. (f) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Chem. Lett.* **2000**, *2*, 104. (g) Chow, Y. L.; Zhou, X.-M.; Gaitan, T. J.; Wu, Z.-Z. *J. Am. Chem. Soc.* **1989**, *111*, 3813. (h) Guss, C. O. *J. Am. Chem. Soc.* **1951**, *73*, 608. (i) Ranade, A. A.; Joseph, A. R.; Kumbhan, V. B.; Paradkar, M. V. *J. Chem. Res., Miniprint* **2003**, *11*, 1175. (j) Bilgic, O.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1233. (k) Das, S.; Thanulingam, T. L.; Rajesh, C. S.; George, M. V. *Tetrahedron Lett.* **1995**, *36*, 1337. (l) Rajesh, C. S.; Thanulingam, T. L.; Das, S. *Tetrahedron* **1997**, *53*, 16817. (m) Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 13596. (n) Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 5964.

(6) (a) Jha, A.; Dimmock, J. R. *Can. J. Chem.* **2003**, *81*, 293. (b) Jha, A.; Padmanilayam, M. P.; Dimmock, J. R. *Synthesis* **2002**, 463.

(7) Jha, A.; Beal, J. *Tetrahedron Lett.* **2004**, *45*, 8999.

(8) Oloo, E. O.; Quail, J. W.; Padmanilayam, M. P.; Dimmock, J. R. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2002**, *58*, o687.

(9) (a) Upadhya, T. T.; Gurunath, S.; Sudalai, A. *Tetrahedron: Asymmetry* **1999**, *10*, 2899. (b) Nerdel, F.; Frank, D.; Lengert, H.-J.; Weyerstahl, P. *Chem. Ber.* **1968**, *101*, 1850. (c) Nerdel, F.; Kaminski, H.; Weyerstahl, P. *Chem. Ber.* **1969**, *102*, 3679. (d) Sirkecioglu, O.; Talinli, N.; Akar, A. *J. Heterocycl. Chem.* **1998**, *35*, 457.

(10) In a typical procedure, a mixture of an appropriate β-hydroxypropionaldehyde (0.01 mol) and a 2-tetralone analogue (0.0105 mol) were stirred in AcOH (ca. 50 mL) at 0 °C. Freshly prepared dry HCl gas was briskly passed through the mixture for 1 h. Stirring was continued at r.t. for 17 h. Then, AcOH was removed under vacuum and the residue was extracted with CH_2Cl_2 (2 × 100 mL) and H_2O (2 × 50 mL). The organic layer was dried and rotary evaporated to dryness to yield crude product, which was purified by column chromatography (silica gel mesh size 230–240; eluent 1–2% EtOAc–hexane). **Spectroscopic Data for a Representative Compound**
Compound **4o**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53 (3 H, s, CH_3), 3.10 and 3.46 (1 H each, d, *J* = 16.2 Hz, $ArCH_a$ and $ArCH_b$), 3.97 (3 H, s, OCH_3), 4.19 and 4.33 (1 H each, d, *J* = 10.5 Hz, OCH_a and OCH_b), 6.99 (1 H, d, *J* = 8.7 Hz, ArH), 7.08 (1 H, m, ArH), 7.15 (1 H, s, ArH), 7.32 (1 H, d, *J* = 6.9 Hz, ArH), 7.39–7.50 (4 H, m, ArH), 7.61 (1 H, d, *J* = 8.7 Hz, ArH), 7.73 (1 H, d, *J* = 8.7 Hz, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$,): δ = 25.00, 35.84, 36.36, 55.75, 74.42, 101.48, 112.70, 115.65, 116.56, 124.80, 126.31, 127.09, 127.91, 129.03, 130.51, 134.82, 146.17, 152.33, 158.81 ppm. IR (KBr): ν = 2963, 1624, 1515, 1233, 1222, 1028, 830, 699 cm^{-1}.

(11) Yamabe, S.; Tsuchida, N.; Yamazaki, S. *J. Comput. Chem.* **2007**, *28*, 1561.

(12) (a) Carey, F. A.In *Organic Chemistry*, 6th ed.; McGraw Hill: New York, **2006**, 362. (b) Westacott, R. E.; Johnston, K. P.; Rossky, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 1006.

(13) Armarego, W. L. F.; Perrin, D. D.In *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: Oxford, **2002**, 223.