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Novel synthesis of 2,2-dialkyl-3-dialkylamino-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans

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Quinone methide
Microwave-assisted synthesis
Cyclization

ABSTRACT

2,2-Dialkyl-3-dialkylamino-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans were prepared from 2-naphthol, a secondary amine, and 3-hydroxy-2,2-dialkylpropanal in the presence of a catalytic amount of *p*-toluenesulfonic acid. This one-pot reaction involves retro-aldol disintegration of 3-hydroxy-2,2-dialkylpropanal followed by formation of a Mannich base intermediate from 2-naphthol, a secondary amine, and formaldehyde (retro-aldol product). This Mannich base then disproportionates into a quinone methide intermediate and the secondary amine is regenerated. It then forms an enamine intermediate with 2,2-dialkylacetaldehyde (another retro-aldol product). Finally, the quinone methide intermediate undergoes electrocyclic ring closure with enamines to produce the title compounds.

3*H*-Naphtho[2,1-*b*]pyrans, also known as 3*H*-benzo[*f*]chromenes, are well documented for their photochromic character.[1–3] This characteristic leads to their application in transition lenses which tint upon exposure to sunlight.[4] Naphthopyrans are also prevalent in numerous natural products with significant biological and medicinal properties.[5,6] They have been shown to exhibit potent mutagenic,[5] cytotoxic,[5,6] anticancer,[7–9] and antiproliferative[10] activities. Hence, synthesizing novel naphthopyran derivatives offers the possibility of uncovering new biological activities and other applications are yet to be found.

Since this investigation primarily deals with novel procedures for the synthesis of 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran derivatives, it is imperative to review previously reported synthetic procedures which were found to generally lack simplicity and satisfactory yields. 2,3-Dihydro-1*H*-naphtho[2,1-*b*]pyran was prepared in 31% yield from 2-allyloxy-1-bromonaphthalene and AIBN, using a modified stannane reagent;[11] conventional Bu_3SnH gave only 17% yield.[12] In a similar endeavor, 1-bromo-2-but-3-enyloxy-naphthalene resulted in formation of 2-methyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran as one of the products.[13] Suzuki et al. published the synthesis of 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran in ~70% yield from 2-allyloxy-1-iodonaphthalene using 9-BBN and palladium dichloride.[14] Use of phosphinic acid, AIBN and $NaHCO_3$ on 2-allyloxy-1-iodonaphthalene leading to same product is also known.[15,16] Chow et al. discovered that singlet excited-state proton transfer on 1-allyl-2-naphthols causes cyclization and results in formation of 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran in 13% yield.[17] In another 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.[18,19] 2,3-Dihydro-1*H*-naphtho[2,1-*b*]pyran was also obtained from 2-naphthol and acrylonitrile by a 6-step reaction sequence in low overall yield.[20] Reaction of 2-naphthol and 3-methylbut-2-enoyl chloride in nitrobenzene and a small amount of anhydrous aluminum chloride led to formation of the corresponding naphthopyranone derivative after 12 days.[21] Various dihydronaphthopyrans were prepared by synthetic manipulations on the double bond of 3,3-dimethyl-3*H*-naphtho[2,1-*b*]pyran.[22] A multi-step 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 involves sodium borohydride reduction followed by a dehydration and di-imide reduction sequence.[23] The same research article also reported the

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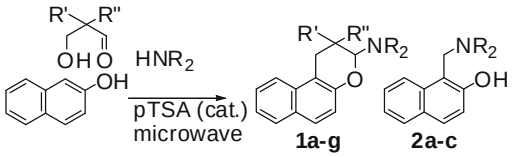
synthesis of 3-ethoxy-2,3-dihydro-3-methyl-1*H*-naphtho[2,1-*b*]pyran from 2-naphthol, methyl iodide, and 1-(*N*,*N*-diethylamino)butan-3-one in dry ethanol.[23] Use of expensive Au(III) to catalyze intramolecular carbon-carbon bond formation in 2-naphthyloxy-propyl triflate or mesylate ester led to formation of 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran in ~90% yield.[24] The group subsequently reported Au(III)-catalyzed intramolecular cycloalkylation of 2-(2-naphthyloxymethyl)oxirane to 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran-2-ol in 76% yield.[25] Multiple step syntheses, poor yields, formation of by-products, and/or use of expensive reagents are some of the serious drawbacks of most of the procedures described above.

In pursuit of molecules with novel carbon skeletons making use of 2-tetralone and 2-naphthol analogs,[26–31] our research group has also developed novel procedures for the one-pot syntheses of 12*H*-benzo[*a*]xanthenes[26] and 2,2-dialkyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans[27] from substituted *ortho*-hydroxy aromatic aldehydes and 2,2-dialkyl-3-hydroxypropanals, respectively, with 2-tetralone analogs under acidic conditions with high yields.

Two synthetic approaches reported in the literature were found to be most closely related to the present investigation.[32-34] One involved reaction of 2-naphthol Mannich bases and enamines to produce 2,2-dialkyl-3-dialkylamino-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans.[32,33] The second one reported a simple method of preparing 2,2-dialkyl-3-dialkylaminonaphtho[2,1-*b*]pyran-1-ols from 2-hydroxy-1-naphthaldehyde and enamines.[34] We herein report a novel microwave-assisted synthesis of 2,2-dialkyl-3-dialkylamino-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans (**1a**–**g**) from 2-naphthol, a secondary amine and 3-hydroxy-2,2-dialkylpropanal in the presence of a catalytic amount of *p*TSA.

The solvent-free microwave-assisted reaction (Scheme 1) between 2-naphthol, 2,2-disubstituted-3-hydroxypropanals, and cyclic secondary amines in the presence of catalytic amounts of *p*TSA resulted in the formation of 2,2-dialkyl-3-dialkylamino-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans (**1a**–**g**) along with 2-naphthol Mannich bases (**2a**–**c**).[35] The physical data of seven reactions involving 2-naphthol are indicated in Table 1.

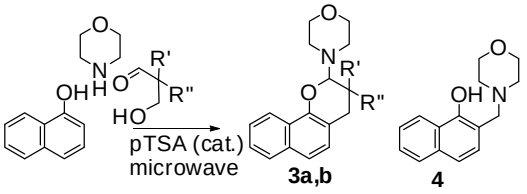
Two reactions were performed using 1-naphthol as the starting material in place of 2-naphthol. Two 3,3-dialkyl-2-morpholino-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran analogs were synthesized (Scheme 2). Physical data of these compounds are presented in Table 2.



Scheme 1. Microwave-assisted reaction of 2,2-dialkyl-3-dialkylamino-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans.

All compounds were completely characterized by spectroscopic means. Compounds **1a**,**b**,**d**–**g**, and **3a**,**b** are new to chemical literature. The NMR data of series **1** compounds would bear substantial resemblance to those of expected isomeric products **5** (Scheme 3, vide infra), unequivocal support of their structure came from X-ray crystal structures of representative compounds **1d** and **1g** (Fig. 1A and B, respectively).[36] As expected, compounds **1e** and **1f** were obtained as diastereomeric mixtures with relatively low diastereoselectivity (de 10–12%) which we wish to study in future.

We originally had expected to synthesize 2,2-dialkyl-1-dialkylamino-2,3-dihydro-naphtho[2,1-*b*]pyrans (**5**) using 2,2-disubstituted-3-hydroxypropanals, 2-naphthol, and cyclic secondary amines utilizing a Mannich reaction-cyclization sequence. Instead, we obtained 2,2-dialkyl-3-dialkylamino-2,3-dihydro-1*H*-naph-

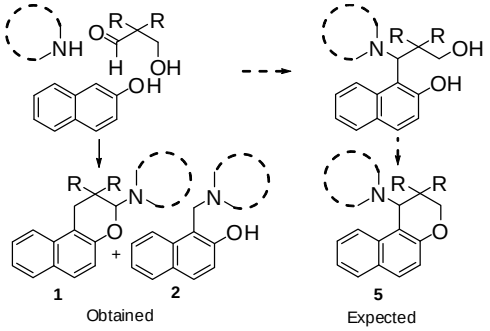


Scheme 2. Microwave-assisted reaction of 3,3-dialkyl-2-morpholino-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyrans.

Table 2
Physical data of 3,3-dialkyl-2-morpholino-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran (**3a**,**b**) and Mannich base **4a**

No	R′	R″	–NR_2	3		4	
				% Yield	mp (°C)	% Yield	m.p (°C)
a	$-CH_3$	$-CH_3$	Morpholino	42	106–107	N.C.	73–74
b	$-CH_2CH_3$	$-CH_2CH_3$	Morpholino	37	Liquid	N.C.	—

N.C. = Obtained but not calculated.



Scheme 3. Expected and obtained products were shown side by side.

Table 1
Physical data of 2,2-dialkyl-3-dialkylamino-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans (**1a**–**g**) and corresponding Mannich bases (**2a**–**c**)

No	R′	R″	–NR_2	1		2	
				% Yield	mp (°C)	% Yield	mp (°C)
a	$-CH_3$	$-CH_3$	Pyrrolidino	45	101–103	42	86–88
b	$-CH_3$	$-CH_3$	Piperidino	57	50–53	33	88–90
c	$-CH_3$	$-CH_3$	Morpholino	57	140–142	40	114–116
d	$-CH_2CH_3$	$-CH_2CH_3$	Morpholino	47	102–104	39	N.R.
e	$-CH_2CH_3$	$-(CH_2)_3CH_3$	Morpholino	48	Liquid	N.C.	N.R.
f	$-CH_3$	$-C_6H_5$	Morpholino	60	Liquid	N.C.	N.R.
g	$-CH_2(CH_2)_3CH_2-$	Morpholino		72	153–155	N.C.	N.R.

N.C. = Obtained but not calculated; N.R. = Not recorded.

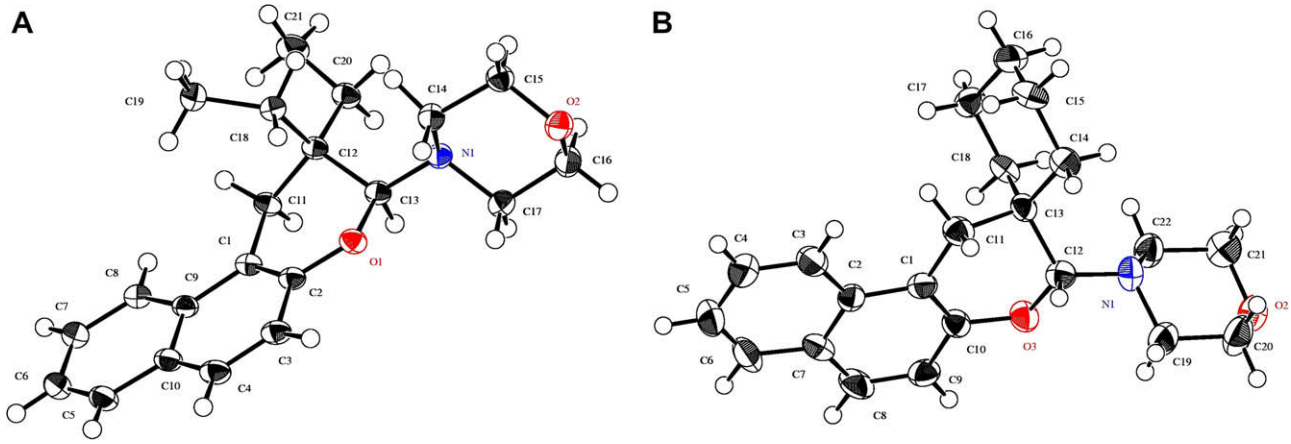


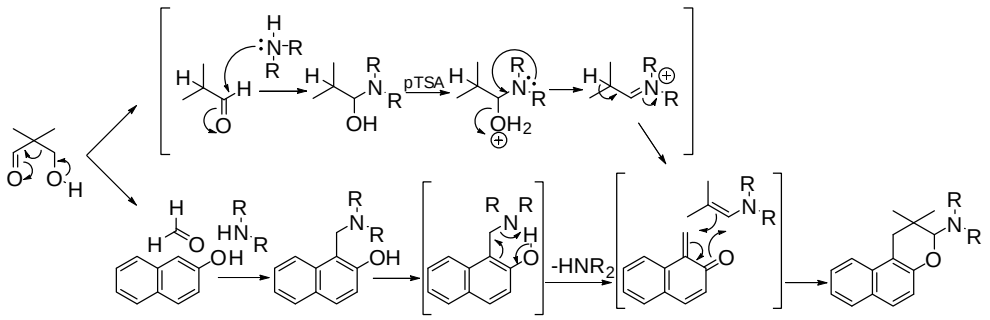
Figure 1. ORTEP diagrams of X-ray crystal structures of **1d** (A) and **1g** (B).

tho[2,1-*b*]pyrans (**1a**–**g**) as one of the products. In addition, 1-dialkylaminomethyl-2-naphthols (**2**) was invariably obtained in all cases (Scheme 3).

At the first instance, it appeared as if the product was formed via a mechanism where the imminium ion formed by the reaction of the amine and the aldehyde is attacked by nucleophilic hydroxyl group of ambidentate 2-naphthol leading to a hemiaminal rather than the nucleophilic C-1 carbon attacking the imminium ion which would have resulted in a Mannich base, as initially expected. A subsequent cyclization–dehydration–aromatization sequence of the hemiaminal intermediate yielding the 2,2-dialkyl-3-dialkylamino-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans under acid catalyzed SN_2-type conditions also appeared reasonable. This mechanism, however, does not explain the formation of Mannich base side products **2a**–**c**. Presence of formaldehyde (or its equivalent) is mandatory for the formation of these side products. This led us to speculate if 2,2-disubstituted-3-hydroxypropanals underwent retro-aldol disproportionation to formaldehyde and 2,2-disubstituted acetaldehyde in situ. Formaldehyde (a non-enolizable aldehyde) is known to give facile reaction with 2-naphthol to produce Mannich bases (**2**) in the presence of secondary amines.[30–32] This evidence of retro-aldol disproportionation led to a reassessment of the mechanism for the formation of compounds **1** as shown in Scheme 3. A report by Strandtmann et al.[32] described the formation of 2,2-dialkyl-3-dialkylamino-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans from 2-naphthol Mannich bases and enamines via deamination followed by cycloaddition. Based on this report, it became apparent that the retro-aldol breakdown products of 2,2-disubstituted-3-hydroxypropanals, namely, formaldehyde and 2,2-disubstituted acetaldehydes, met different fates resulting in facile formation of 2-naphthol Mannich bases and enamines, respectively. This is expected as non-enolizable formaldehyde will be more amenable to Mannich reaction while enolizable 2,2-disubstituted acetaldehydes will be more so to the formation of enamines. Under the employed reaction conditions, the Mannich bases deaminated to quinone methides. Perycyclic cycloaddtion between electron deficient quinone methide and electron rich enamine resulted in 2,2-dialkyl-3-dialkylamino-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans (**1a**–**g**) with aromatization being the driving force (Scheme 4).

To substantiate this mechanistic pathway, a *p*TSA-catalyzed four-component reaction involving 2-naphthol, paraformaldehyde, isobutyraldehyde, and morpholine (1 M equiv each) was carried out under microwave-assisted conditions identical to the original three component reaction. This indeed led to the formation of 2,2-dimethyl-3-morpholino-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran (**1c**, 52%) and 1-morpholinomethyl-2-naphthol (**2c**, 43%). Reaction of 2-naphthol, 2,2-dimethyl-3-hydroxypropanal, and morpholine was also carried out using conventional conditions. The mixture was dissolved in DMF and refluxed for 3 h. Compounds **1c** and **2c** were obtained in 22% and 38% yields, respectively. Based on these results, the microwave-assisted procedure was found to be a more efficient method to synthesize 2,2-dialkyl-3-dialkylamino-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans.

In summary, the synthesis of novel 2,2-dialkyl-3-dialkylamino-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans from 2,2-disubstituted-3-hydroxypropanals, 2-naphthol, and cyclic secondary amines was achieved in moderate to good yields under controlled microwave heating in the presence of *p*TSA. The overall mechanism of formation of the title compounds (**1a**–**g**) involves two disproportionation steps (retro-aldol and deamination of Mannich bases) and a pericyclic cycloaddition step. A simpler *p*TSA-catalyzed four-component reaction was also developed to produce the title compounds which validated the proposed mechanism.



Scheme 4. Most plausible mechanism of formation of 2,2-dimethyl-3-dialkylamino-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.083.

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35. In a typical procedure, a mixture of 1- or 2-naphthol (0.01 mol), an appropriate β-hydroxypropionaldehyde (0.0105 mol), and a secondary amine (0.0105 mol) with catalytic amount of *p*-toluenesulfonic acid (*p*TSA) were reacted under neat microwave conditions (CEM Discover S-Class) in a closed vessel at 190 °C for 5 min. The crude product was purified by column chromatography (silica gel mesh size 230–400; eluent 5–10% MeOH/DCM). Data for a representative compound is presented here. *Compound* **1a**: Yield: 45%; mp: 101–103 °C. ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.22 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.81–1.85 (m, 4H, 2 × $-CH_2$), 2.94 (d, J = 5.4 Hz, 2H, $ArCH_2$), 3.00–3.05 (m, 2H, NCH_{2a}), 3.10–3.15 (m, 2H, NCH_{2b}), 4.77 (s, 1H, OCHN), 7.13 (d, J = 9.0 Hz, 1H, Ar-H), 7.37 (t, J = 7.8 Hz, 1H, Ar-H), 7.52 (t, J = 7.8 Hz, 1H, Ar-H), 7.67 (d, J = 8.7 Hz, 1H, Ar-H), 7.81 (d, J = 8.7 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz; CDC_{l3}): δ 23.48, 25.19, 27.98, 33.48, 39.64, 49.16, 95.69, 113.15, 119.10, 122.24, 123.24, 126.52, 128.00, 128.80, 129.19, 133.60, 153.13. IR (KBr; ν_{max}): 3060, 2964, 2871, 1623, 1468, 1219, 1161, 810, 744 cm^{-1}. UV (EtOH, λ_{max}): 233, 277, 333 nm. ESI HRMS (amu): measured for $C_{19}H_{23}NO$ $[M+H]^+$ 282.1834; actual $[M+H]^+$ 282.1858.
36. CCDC nos. 700816 and 700817 contain the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif).