Pergamon

Tetrahedron Letters 42 (2001) 6381–6384

TETRAHEDRON LETTERS

$LiBF_4$-catalyzed formation of fused pyrano- and furanobenzopyrans†

J. S. Yadav,[a,*] B. V. Subba Reddy,[a] Ch. Madhuri,[a] G. Sabitha,[a] B. Jagannadh,[a] S. Kiran Kumar[b] and A. C. Kunwar[b]

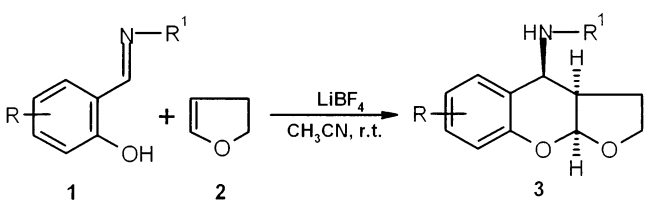
[a]*Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500007, India*
[b]*Centre for Nuclear Magnetic Resonance, Indian Institute of Chemical Technology, Hyderabad 500007, India*

Received 17 April 2001; accepted 12 July 2001

Abstract—Lithium tetrafluoroborate efficiently catalyzes an unusual cyclization of *o*-hydroxybenzaldimines with 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran at ambient temperature to afford a class of new pyrano- and furanobenzopyran derivatives in excellent yields with high diastereoselectivity. © 2001 Elsevier Science Ltd. All rights reserved.

2*H*-1-Benzopyrans (2*H*-chromenes) and 3,4-dihydro-2*H*-1-benzopyrans (chromans) have attracted much synthetic interest because of the biological activity[1,2]of naturally occurring representatives. 4-Aminobenzopyrans and their derivatives are found to exhibit a wide range of biological activities[3,4] including antihypertensive and antiischemic behaviour. Particularly, fused tetrahydropyranobenzopyran derivatives are frequently found in naturally occurring bioactive molecules and direct methods for their synthesis are highly desired.[5] Recently, angularly fused pyranobenzopyrans have been reported by intramolecular cycloaddition of *o*-quinonemethides using protic acid as a catalyst.[6] However, there is no report on the synthesis of linearly fused chromans from *o*-hydroxybenzaldimines and cyclic enol ethers. Recently, lithium tetrafluoroborate in acetonitrile (LTAN) has received much attention as a powerful reaction medium for effecting various transformations[7,8] including the hydrolysis of acetals, desilylation of ethers, dithioacetalization of aldehydes and glycosidation reactions. Unlike ClO_4^-, the counterion BF_4^- is non-nucleophilic and non-oxidizing and hence it provides convenient reaction and work-up conditions.

In this report, we describe a new and highly efficient protocol for the synthesis of fused pyrano- and furanochromans using a catalytic amount of $LiBF_4$ in acetonitrile. The treatment of salicylaldehyde Schiffs base with 2,3-dihydrofuran[9] in the presence of lithium tetrafluoroborate at ambient temperature affords the *cis*-fused furanochroman in 90% yield (Scheme 1). Similarly, several *o*-hydroxybenzaldimines (formed in situ from *o*-hydroxybenzaldehydes and anilines in the presence of anhydrous Na_2SO_4 in acetonitrile) reacted well to give the corresponding *cis*-fused acetals in excellent yields. The reactions proceed smoothly at ambient temperature with high diastereoselectivity. In all reactions the product was obtained as a single isomer, the structure of which was confirmed by detailed ^1H NMR and NOESY studies. The six-membered tetrahydropyran and five-membered tetrahydrofuran rings are *cis* fused, as depicted by the coupling constant $J_{3-4}=5.4$ Hz between H4 (δ 5.89)–H3 (δ 3.11) and the presence of a strong cross peak between them in the NOESY spectrum of the product **3a**. Also, $J_{3-5}=4.8$ Hz (H5-δ 4.99) and the presence of a NOE cross peak, H4–H5, support that H5 is *cis* to H3. Molecular mechanics calculations indicate a structure with the six-membered pyran ring in the boat conformation, Fig. 1, which also depicts the important NOEs in assigning the stereochemistry of **3a**.



1 2 3

Scheme 1.

Keywords: lithium tetrafluoroborate; *o*-hydroxyaldimines; cyclic enol ethers; *cis*-fused chromans.

* Corresponding author. Fax: +91-40-7170512; e-mail: yadav@iict.ap.nic.in

† IICT communication No. 4775.

PII: S0040-4039(01)01257-6

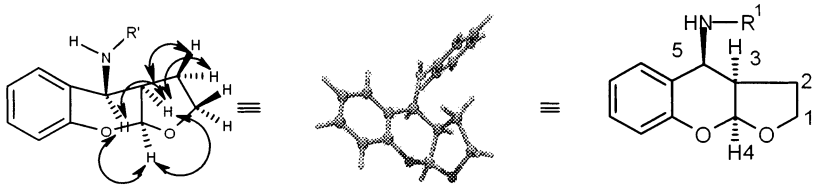
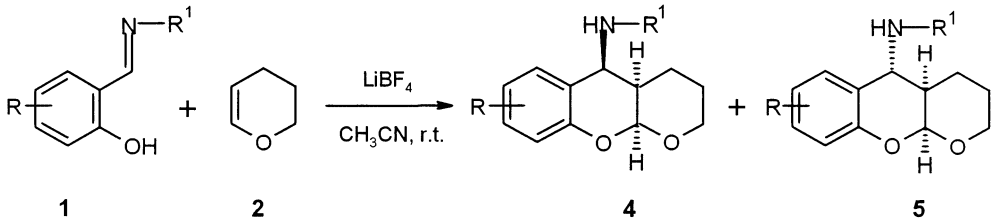


Figure 1. Important NOEs, the energy-minimized structure and the chemical structure of **3a**.



Scheme 2.

Table 1. $LiBF_4$-catalyzed formation of furano- and pyranochromans[a]

Entry	R	R^1	Enol ether	Reaction time (h)	Yield (%)[b]	Product ratio[c]
a	H	C_6H_5		2.5	90	100:0
b	H	C_6H_5		3.0	87	80:20
c	5-Cl	C_6H_5		5.0	81	100:0
d	H	4-MeC_6H_4		6.0	78	70:30
e	H	2-MeC_6H_4		4.0	85	10:90
f	3-OEt	C_6H_5		3.0	88	100:0
g	H	4-MeC_6H_4		2.5	90	100:0
h	H	2-Br-4-MeC_6H_3		4.0	80	40:60
i	H	4-MeC_6H_4		3.5	83	100:0
j	3-OEt	4-ClC_6H_4		4.0	78	100:0
k	H	4-$OMeC_6H_4$		4.5	84	100:0
l	3-OMe	4-MeC_6H_4		3.0	90	100:0
m	H	4-ClC_6H_4		3.5	81	100:0
n	3-OMe	C_6H_5		4.0	85	100:0

[a] Isolated and unoptimized yields after column chromatography.
[b] Product ratio was determined by the ^1H NMR spectrum of the crude product.

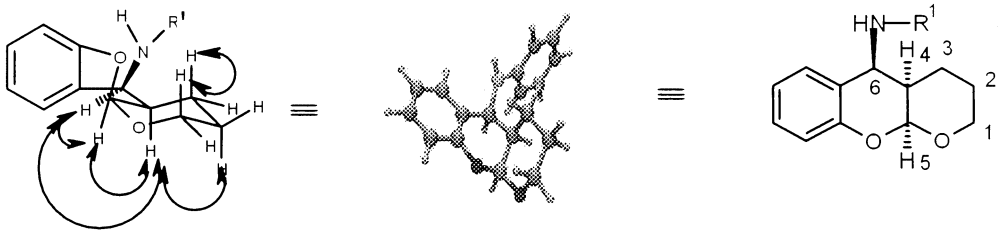


Figure 2. Important NOEs, the energy-minimized structure and the chemical structure of **4b**.

Further, the treatment of *o*-hydroxyaldimines with 3,4-dihydro-2*H*-1-pyran in the presence of $LiBF_4$ in acetonitrile resulted in the formation of fused pyranochromans as a mixture of **4** and **5** in high yields (Scheme 2).

The reactions are clean and highly diastereoselective, affording the corresponding *cis*-fused acetal **4** with minor amounts of the other isomer **5**. However, in the case of *ortho* substituted *N*-arylimines, product **5** was obtained as the major isomer with a trace amount of **4** (entry e, Table 1). The ratio of **4** and **5** was determined by the ^1H NMR spectrum of the products. The assignment of the stereochemistry of product **4b** was based on the coupling constants and NOE cross peaks in the NOESY spectrum. In this product also, like product **3a**, the two six-membered rings are *cis* fused. The coupling constants $J_{4-5}=2.5$ Hz and $J_{4-6}=5.5$ Hz (H5 δ 5.57, H6 δ 5.01, H4 δ 2.51) and the presence of NOE cross peaks H4–H5, H5–H6 and H4–H6 again show that these protons are on the same side of the ring. While the middle six-membered ring is in the half chair conformation, the tetrahydropyran ring takes a chair conformation, which is consistent with the presence of NOE cross peaks (between H1ax–H3ax and H2ax–H4) and couplings ($J_{1ax-2ax}=12.3$ Hz, $J_{3ax-4}=12.9$ Hz) (Fig. 2). The product **5e** differs from **4b** having a different configuration at C_6. This is supported by cross peaks between H3eq–H6, H3ax–H6 and H5–NH, as well as the absence of cross peaks between H5–H6 (Fig. 3), which is further supported by molecular mechanics calculations.[10]

The reactions probably proceed through the activation of the imine by a lithium ion, followed by addition and subsequent cyclization of the enol ether resulting in the formation of the fused acetal (Scheme 3).

The reaction conditions are very mild so that no side products or decomposition of the products is observed. No additives or acidic promoters are required to promote the reaction. The procedure does not require anhydrous solvents or stringent reaction conditions. Due to the neutral reaction conditions, this method is compatible with acid sensitive aldehydes and unstable imines.[11] It is of interest to note that the reaction of cyclic enol ethers with aldimines without a hydroxyl group at the *ortho* position gave the corresponding pyrano and furanoquinolines in high yields. The best results were obtained when acetonitrile was used as the solvent. Several examples illustrating this novel and rapid procedure for the synthesis of fused chromans are summarized in Table 1.

In summary, we have demonstrated a novel and practical method for the synthesis of *cis* fused pyrano- and furanobenzopyrans using a catalytic amount of lithium tetrafluoroborate under neutral conditions. In addition to its simplicity and mild reaction conditions, this procedure has advantages of high yields of products, easy availability and flexibility of starting materials, short reaction times, operational simplicity, useful diastereoselectivity and simple experimental and work-up procedures, which makes it a very useful and attractive process for the synthesis of fused benzopyrans.

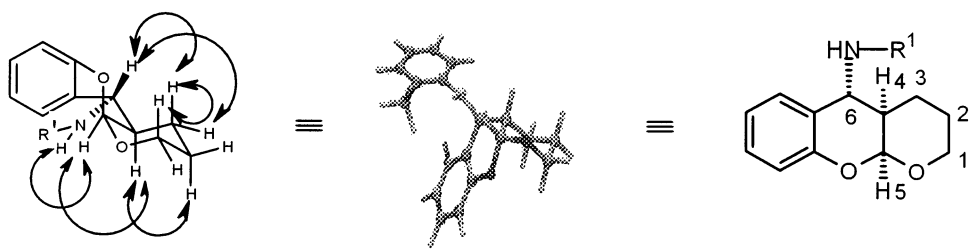
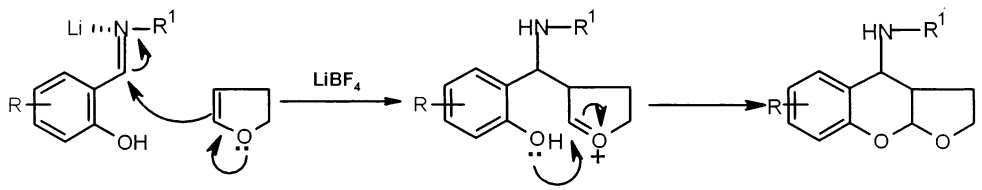


Figure 3. Important NOEs, the energy-minimized structure and the chemical structure of **5e**.



Scheme 3.

Acknowledgements

B.V.S., Ch.M. and S.K.K. thank CSIR, New Delhi for the award of fellowships.

References

1. Hepworth, J. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R.; Rees, C. W.; Eds.; Pergamon: Oxford, 1984; Vol. 3, pp. 737–883.
2. (a) Schweizer, E. E.; Meeder-Nycz, O. In *Chromenes, Chromanes, Chromones*; Ellis, G. P., Ed.; Wiley Interscience: New York, 1977; pp. 11–139; (b) Bowers, W. S.; Ohta, T.; Cleere, J. S.; Marsella, P. A. *Science* **1976**, *193*, 542.
3. (a) Nicolaou, K. C.; Around, P.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G. Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939; (b) Evans, J. M.; Fake, C. S.; Hamilton, T. C.; Poyser, R. H.; Watts, E. A. *J. Med. Chem.* **1990**, *33*, 493.
4. (a) Burgard, A.; Lang, H.-J.; Gerlach, U. *Tetrahedron* **1999**, *55*, 7555; (b) Evans, J. M.; Fake, C. S.; Hamilton, T. C.; Poyser, R. H.; Showell, G. A. *J. Med. Chem.* **1984**, *27*, 1127; (c) Evans, J. M.; Fake, C. S.; Hamilton, T. C.; Poyser, R. H.; Watts, E. A. *J. Med. Chem.* **1983**, *26*, 1582.
5. (a) Davis, M.; Pettett, M. *Aust. J. Chem.* **1979**, *32*, 369; (b) Bravo, P.; Ticozzi, C.; Maccioni, A. M.; Traldi, P. *J. Heterocycl. Chem.* **1987**, *24*, 895.
6. Miyazaki, H.; Honda, K.; Asami, M.; Inoue, S. *J. Org. Chem.* **1999**, *64*, 9507.
7. Yadav, J. S.; Reddy, B. V. S.; Pandey, S. K. *Synlett* **2001**, *2*, 38.
8. Babu, B. S.; Balasubramanian, K. K. *Acros Org. Acta* **2000**, *7*, 1.
9. Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15.
10. (a) Goto, H.; Osawa, E. *J. Chem. Soc., Perkin Trans 2* **1993**, 187; (b) PC MODEL, Serena Software BOX 3076, Bloomington, IN.
11. **Experimental procedure**: A mixture of *o*-hydroxybenzaldimine (5 mmol), dihydrofuran or dihydropyran (6 mmol) and lithium tetrafluoroborate (0.5 mmol) in acetonitrile (10 mL) was stirred at ambient temperature for the appropriate time. After completion of the reaction, as indicated by TLC, the reaction mixture was quenched by addition of water (10 mL) and extracted with ethyl acetate (2×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and the resulting product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 0.5:95) to afford pure *cis*-fused acetal. Spectral data for product **3a**: solid, mp 95°C, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.62 (m, 1H, H2, J=8.2, 8.7, 12.2 Hz), 1.92 (m, 1H, H2′, J=4.0, 7.5, 12.2 Hz), 3.11 (dddd, 1H, H3, J=4.8, 5.4, 8.7, 10.6 Hz), 3.80 (brs, NH), 3.85 (ddd, 1H, H1, J=8.7, 8.2, 7.5 Hz), 3.92 (ddd, 1H, H1′, J=8.7, 8.7, 4.0 Hz), 4.99 (d, 1H, H5, J=4.8 Hz), 5.89 (d, 1H, H4, J=5.4 Hz), 6.65 (d, 2H, J=7.8 Hz), 6.67 (t, 1H, J=7.3 Hz), 6.85–6.95 (m, 2H), 7.15–7.25 (m, 3H), 7.30 (d, 1H, J=7.3 Hz). ^{13}C NMR (50 MHz, $CDCl_3$, proton decoupled) δ: 24.0, 43.80, 48.85, 68.0, 96.2, 102.4, 113.8, 117.3, 118.4, 122.0, 124.7, 126.0, 128.5, 130.0, 147.5, 153.8. EIMS: m/z. 267 M^+, 197, 145, 107, 91, 77, 71, 55, 41. **4b**: solid, mp 110°C, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.33–1.71 (m, 4H, H2, H2′, H3, H3′), 2.51 (dddd, 1H, H4, J=2.5, 5.5, 4.2, 12.9 Hz), 3.76 (ddt, 1H, H1, J=1.7, 1.7, 4.8, 11.3 Hz), 3.80 (brs, NH), 4.02 (dddd, 1H, H1′, J=2.9, 11.3, 12.3 Hz), 5.01 (d, 1H, H6, J=5.5 Hz), 5.57 (d, 1H, H5, J=2.5 Hz), 6.75 (d, 2H, J=8 Hz), 6.78 (t, 1H, J=7.8 Hz), 6.90 (m, 2H), 7.18–7.25 (m, 3H), 7.40 (d, 1H, J=8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, proton decoupled) δ: 17.08, 21.74, 24.17, 34.8, 50.9, 60.9, 61.77, 94.6, 96.3, 112.6, 113.2, 116.4, 118.0, 121.1, 126.7, 129.0, 129.5, 129.6. EIMS: m/z: 281 M^+, 197, 145, 85, 77, 55, 41. **5e**: solid, mp 132°C, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.30–1.75 (m, 4H, H2, H2,′ H3, H3′), 2.06 (s, 3H, CH_3), 2.35 (dddd, 1H, H4, J=2.4, 3.0, 4.2, 12.3 Hz), 3.65 (brs, NH), 3.76 (m, 1H, H1, J=2.2, 4.3, 11.4 Hz), 4.03 (dt, 1H, H1′, J=2.9, 11.4, 11.5 Hz), 4.33 (d, 1H, H6, J=3.0 Hz), 5.45 (d, 1H, H5, J=2.4 Hz), 6.60–6.75 (m, 2H), 6.95–7.05 (m, 2H), 7.15–7.30 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$, proton decoupled) δ: 17.68, 21.8, 24.4, 24.5, 36.7, 53.4, 61.0, 61.7, 94.7, 96.8, 109.5, 117.0, 117.5, 120.8, 121.3, 127.1, 129.5, 130.4, 130.6.