Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 8439–8441
Tetrahedron Letters

Furan ring opening–isochromene ring closure: a new approach to isochromene ring synthesis

Alexander V. Butin,[a,*] Vladimir T. Abaev,[b] Vladimir V. Mel'chin[a] and Artem S. Dmitriev[a]

[a]*Kuban State University of Technology, Moskovskaya st. 2, Krasnodar 350072, Russia*
[b]*North-Ossetian State University, Vatutina st. 46, Vladikavkaz 362025, Russia*

Received 15 June 2005; revised 30 August 2005; accepted 9 September 2005
Available online 17 October 2005

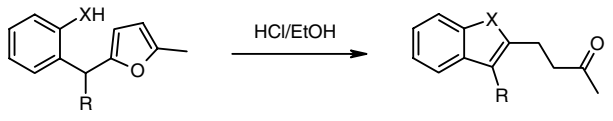
Abstract—A new approach toward the synthesis of 1*H*-isochromenes based on the recyclization of the furan ring in the corresponding *ortho*-hydroxymethylbenzylfurans is described.

The isochromene framework is a frequent structural motif in naturally occurring molecules. For example, flaccidin isolated from the orchids *Dendrobium amoenum* and *Coelogyne flaccida* includes an isochromene framework.[1a] A number of compounds isolated from *Cannabis sativa* also can be viewed as isochromene derivatives.[1b] The roots and the stem of a tree *Ulmus davidiana* (widespread in Korea) are used in oriental medicines for the treatment of inflammations, edema, and stomach cancer. Natural sesquiterpenoids isolated from *U. davidiana* also incorporate an isochromene fragment in their structure.[1c] Hence there is a continuing interest in the elaboration of new routes to the isochromene ring as well as to new interesting derivatives of this heterocyclic system.

Few approaches exist for the construction of the isochromene ring. For example, a rather simple method starting from homophthalic acid was reported.[2] Monophosphonium salts derived from α,α′-dibromoxylene were reacted with sodium carboxylates giving rise to chromene derivatives.[3] Recently, palladium catalyzed intramolecular cyclization of 2-alkynylbenzyl alcohols,[4a] 2-allylbenzyl alcohols,[4b] or allyl-2-bromobenzyl alcohols[4c] was reported. The synthesis of the isochromene ring is also possible via cyclization of *cis*-acyl-*ortho*-quinodimethanes.[5] Chatterjea[6] proposed the synthesis of 1*H*-isochromene by reduction of 1*H*-1-isochromenone via its open form with subsequent cyclization to 1*H*-chromene. In essence, this method is based on the intramolecular cyclization of a 2-methylenehydroxybenzyl carbonyl compound formed in situ.

We are involved in the development of a general access to the synthesis of benzannelated heterocycles based on the recyclization of *ortho*-substituted benzylfurans.[7] Furan ring opening under protolytic conditions, when the furan ring acts as a 1,4-dicarbonyl equivalent is well known.[8] We have found that the presence of suitable nucleophiles at *ortho*-positions of the benzene ring of benzylfurans dramatically facilitates furan ring cleavage. By varying the *ortho*-substituent in the benzylfuran, we succeeded in obtaining derivatives of benzofuran,[9] indole,[10] isochromenone[11] and isoquinolone[12] (Scheme 1). It is worth mentioning that the recyclization step in *ortho*-substituted phenyldifuryl methanes is often accompanied by secondary cyclization of the resulting butan-3-one fragment onto the β-position of the second furan ring, thus leading to the formation of condensed tetracyclic molecules.[7,11,12]

Pursuing our methodology for the synthesis of the benzannelated heterocycles, we studied the behavior of

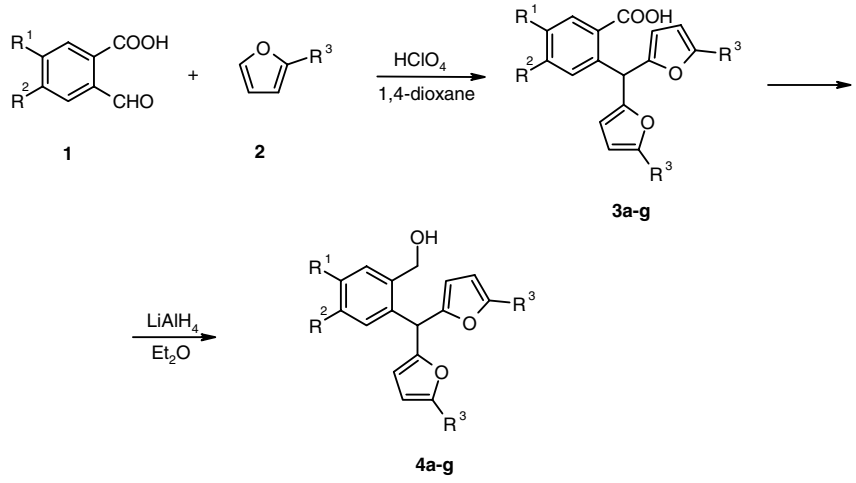


X = O, NTs, COO, CON

Scheme 1.

Keywords: Furan; Recyclization; 1*H*-Isochromene.
* Corresponding author. Tel.: +7 (861) 2559556; e-mail: alexander_butin@mail.ru

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.09.056



Scheme 2.

ortho-hydroxymethylbenzylfurans with the standard recyclization conditions, namely reflux in ethanol saturated with hydrogen chloride.

2-Carboxybenzylfurans[13] **3** were obtained by condensation of 2-formylbenzoic acid derivatives **1** with 2-alkylfurans **2** in dry 1,4-dioxane at 65–70 °C in the presence of a catalytic amount of 70% perchloric acid (Scheme 2). Reduction of the carboxy group of compounds **3** with lithium aluminum hydride gave the corresponding benzyl alcohols **4**.[14]

Treatment of compounds **4** with a saturated solution of hydrogen chloride in ethanol afforded tetracyclic isochromene derivatives **6**.[15] Like the analogous recyclizations to isocoumarin and isoquinolone derivatives,[11,12] no intermediate ketones **5** were isolated (Scheme 3, Table 1).

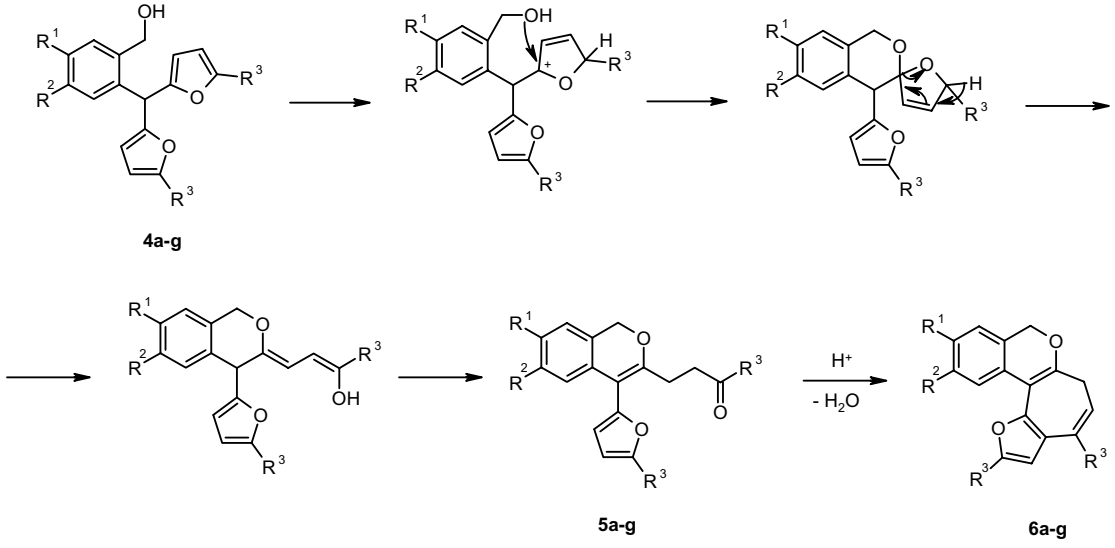
In conclusion, we note that the method described in this letter is potentially very general because the synthesis of a wide number of 1*H*-isochromene derivatives is possible by varying the R^1–R^3substituents.

Table 1. Isochromene synthesis via recyclization of compounds **4**

3, **4**, **6**	R^1	R^2	R^3	Yield (%)		
				3	**4**	**6**
a	H	H	Me	68	91	63
b	Br	H	Me	70	93	61
c	Cl	H	Me	72	96	66
d	H	Br	Me	75	72	57
e	H	Cl	Me	78	69	55
f	OCH_3	H	Me	65	85	70
g	Br	H	Et	67	93	59

Acknowledgements

Financial support was provided by Bayer HealthCare AG and the Russian Foundation of Basic Research (Grant 03-03-32759).



Scheme 3.

References and notes

1. (a) Majumder, P. L.; Guha, S.; Sen, S. *Phytochemistry* **1999**, *52*, 1365–1369; (b) Papadakis, D. P.; Salemink, C. A.; Alikaridis, F. J.; Kephalas, T. A. *Tetrahedron* **1983**, *39*, 2223–2225; (c) Kim, J.-P.; Kim, W.-G.; Koshino, H.; Jung, J.; Yoo, I.-D. *Phytochemistry* **1996**, *43*, 425–430.
2. Cottet, F.; Cottier, L.; Descotes, G. *Synthesis* **1987**, 497–498.
3. Begasse, B.; Hercouet, A.; Le Corre, M. *Tetrahedron Lett.* **1979**, *20*, 2149–2150.
4. (a) Gabriele, B.; Salerno, G.; Fazio, A.; Pittelli, R. *Tetrahedron* **2003**, *59*, 6251–6259; (b) Giles, R. G. F.; Green, I. R.; Taylor, C. P. *Tetrahedron Lett.* **1999**, *40*, 4871–4872; (c) Shi, L.; Narula, C. K.; Mak, K. T.; Kao, L.; Xu, Y.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 3894–3900.
5. Hug, R.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1972**, *55*, 10–15.
6. (a) Chatterjea, J. N. *Chem. Ber.* **1958**, *91*, 2636–2638; (b) Chatterjea, J. N.; Banerjee, B. K.; Jha, H. C. *Chem. Ber.* **1965**, *98*, 3279–3285.
7. See the following review: Butin, A. V.; Abaev, V. T. *Izvest. AN. Seriya Khim.* **2001**, 1436–1443.
8. See the following reviews: (a) Dean, F. M. *Adv. Heterocycl. Chem.* **1982**, *30*, 167–238; (b) Dean, F. M. *Adv. Heterocycl. Chem.* **1982**, *31*, 237–344; (c) Piancatelli, G.; D'Auria, M.; D'Onofrio, F. *Synthesis* **1994**, 867–889.
9. (a) Butin, A. V.; Krapivin, G. D.; Zavodnik, V. E.; Kul'nevich, V. G. *Khim. Geterotsikl. Soedin.* **1993**, 616–626; (b) Abaev, V. T.; Gutnov, A. V.; Butin, A. V. *Khim. Geterotsikl. Soedin.* **1998**, 603–607; (c) Gutnov, A. V.; Butin, A. V.; Abaev, V. T.; Krapivin, G. D.; Zavodnik, V. E. *Molecules* **1999**, *4*, 204–218; see the following review: (d) Butin, A. V.; Gutnov, A. V.; Abaev, V. T.; Krapivin, G. D. *Molecules* **1999**, *4*, 52–61.
10. Butin, A. V.; Stroganova, T. A.; Lodina, I. V.; Krapivin, G. D. *Tetrahedron Lett.* **2001**, *42*, 2031–2033.
11. Gutnov, A. V.; Abaev, V. T.; Butin, A. V.; Dmitriev, A. S. *J. Org. Chem.* **2001**, *66*, 8685–8686.
12. Abaev, V. T.; Osipova, A. A.; Butin, A. V. *Khim. Geterotsikl. Soedin.* **2001**, 849–850.
13. A typical procedure is as follows: To a solution of 5-bromo-2-formylbenzoic acid (5 g, 22.0 mmol) in 35 ml of 1,4-dioxane, 0.065 ml of 70% $HClO_4$ and 5.90 ml (66.0 mmol) of 2-methylfuran were added. The reaction mixture was maintained at 70 °C for 15 min until completion of the reaction (TLC monitoring). The mixture was poured into water, and the resulting precipitate was filtered off, washed with a little methylene chloride, and recrystallized from acetone–ethanol to give **3b**. Yield (5.8 g, 70%), white crystals. Mp = 226–227 °C; Anal. found: C, 57.58; H, 4.10. $C_{18}H_{15}BrO_4$ requires: C, 57.62; H, 4.03; ν_{max} (KBr): 1699 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 2.25 (6H, s, CH_3), 5.88 (4H, s, H_{Fur}), 6.58 (1H, s, C*H*), 7.24 (1H, d, $J = 8.3$ Hz, H_{Ar}), 7.63 (1H, dd, $J = 2.0$, 8.3 Hz, H_{Ar}), 8.19 (1H, d, $J = 2.0$ Hz, H_{Ar}).
14. A typical procedure is as follows: To a cooled suspension (−3 to 0 °C) of **3b** (15 g, 40.0 mmol) in 225 ml of anhydrous diethyl ether, $LiAlH_4$ (3.19 g, 80.0 mmol) was added slowly with vigorous stirring. After the reaction was complete (TLC monitoring), the resulting suspension was poured into water, acidified with HCl to pH 6–7 and extracted with ethyl acetate. The combined extracts were dried over anhydrous Na_2SO_4, purified with active charcoal and the solvent was evaporated under reduced pressure. The residue was recrystallized from hexane. Yield of **4b** 13.4 g, (93%), colorless crystals. Mp 75–77 °C; Anal. found: C, 59.98; H, 4.61. $C_{18}H_{17}BrO_3$ requires: C, 59.85; H, 4.74; ν_{max} (KBr): 3261 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 1.66 (1H, br s, O*H*), 2.25 (6H, s, CH_3), 4.72 (2H, s, CH_2), 5.61 (1H, s, C*H*), 5.85 (2H, d, $J = 3.2$ Hz, 3-H_{Fur}), 5.88 (2H, d, $J = 3.2$ Hz, 4-H_{Fur}), 7.05 (1H, d, $J = 8.3$ Hz, H_{Ar}), 7.39 (1H, dd, $J = 2.1$, 8.3 Hz, H_{Ar}), 7.60 (1H, d, $J = 2.1$ Hz, H_{Ar}).
15. A typical procedure is as follows: A mixture of **4b** (12 g, 33.0 mmol), 48 ml of ethanol saturated with hydrogen chloride (100 g HCl in 200 g ethanol) and 150 ml of the ethanol was refluxed for 20 min. After completion of the reaction (TLC monitoring), the reaction mixture was poured into water, neutralized with sodium carbonate, and extracted with ethyl acetate. The extract was dried over Na_2SO_4, and the solvent was evaporated to dryness. The resulting oil was dissolved in 100–150 ml of hexane under reflux with addition of activated charcoal and then filtered through a pad of silica gel. The solution was then left in a refrigerator overnight and the resulting precipitate filtered off. Yield of **6b** 6.9 g (61%) colorless crystals. Mp 110–112 °C; Anal. found: C, 62.82; H, 4.48. $C_{18}H_{15}BrO_2$ requires: C, 62.99; H, 4.41; δ_H (200 MHz, $CDCl_3$): 2.05 (3H, s, CH_3), 2.44 (3H, s, CH_3), 2.66 (2H, d, $J = 6.7$ Hz, CH_2), 4.97 (2H, s, CH_2), 5.28 (1H, t, $J = 6.7$ Hz, =C*H*), 6.22 (1H, s, H_{Fur}), 7.21 (1H, d, $J = 2.1$ Hz, H_{Ar}), 7.43 (1H, dd, $J = 2.1$, 8.4 Hz, H_{Ar}), 7.87 (1H, d, $J = 8.4$ Hz, H_{Ar}).