Letters to the Editor

A new approach to isochromanes

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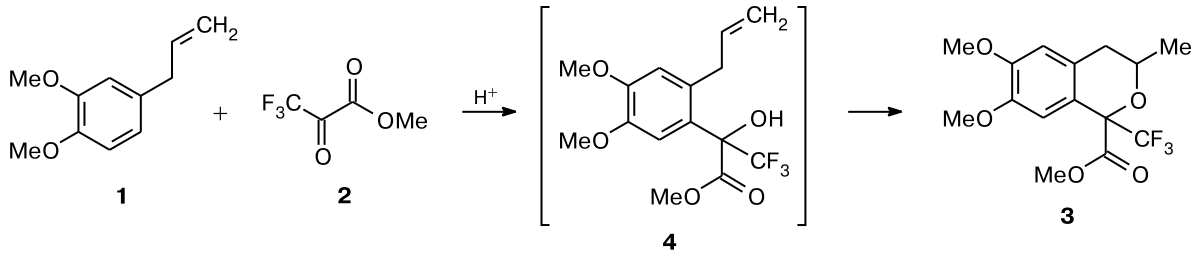
Some isochromane derivatives exhibit hypotensive,[1] antitumor,[2] and growth-regulating[3] activities; some others have a specific effect on the dopaminergic system.[4]

The two most commonly used approaches to the formation of the pyran ring of isochromanes are (1) cyclization of β-phenylethanols with aldehydes in the presence of HCl[5—7] and (2) base-catalyzed cyclization of various 2-allylbenzylic alcohols.[8,9] Despite the high yields of the reaction products, the starting compounds for the final cyclization step are difficult to obtain. The multistep synthesis involving the high-temperature Claisen and Fries rearrangements and the use of gaseous HCl make the above methods labor consuming and little (if any) success should be expected in the case of labile complex substrates.

The distinctive features we have found in reactions of polyfluoro carbonyl compounds with phenols,[10] polyphenols, and their ethers[11] form the basis of a new approach to isochromanes.

A reaction of methyleugenol (**1**) with methyl trifluoropyruvate (**2**)[12] directly gives isochromane derivative **3** (Scheme 1). Apparently, intermediate benzylic alcohol **4** undergoes cyclization involving the allyl substituent.

Scheme 1



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The reaction in aprotic solvents in the presence of a slight excess of oxo ester **2** and catalytic amounts of CF_3SO_3H at 20 °C is completed in 1 h.

The scope of this method and the possibility of employing other carbonyl-containing reactants and catalysts are being refined. The discovered reaction can serve as a convenient tool for modification of the components of essential oils of plants such as myristicin, apiol, dillapiol,[13] and other natural allyl-substituted polyphenols.

^1H and ^{19}F NMR spectra were recorded on a Bruker AM-300 instrument (300.13 and 282.40 MHz, respectively) in $CDCl_3$ with Me_4Si (^1H) as the internal standard and with CF_3CO_2H (^{19}F) as the external standard. Mass spectra were measured on a Finnigan MAT INCOS 50 quadrupole mass spectrometer (direct inlet probe, 70 eV).

Methyl 6,7-dimethoxy-3-methyl-1-trifluoromethylisochromane-1-carboxylate (3). 1-Allyl-3,4-dimethoxybenzene (**1**) (178 mg, 1 mmol), methyl trifluoropyruvate[13] (**2**) (200 mg, 1.3 mmol), and several drops of CF_3SO_3H were mixed in anhydrous CH_2Cl_2 (2 mL). The reaction mixture was stirred at ~20 °C for 1 h, neutralized with 5% Na_2CO_3, and washed with water. The organic layer was separated, dried with Na_2SO_4, and passed through a short column with silica gel. The solvent was removed on a rotary evaporator. The resulting, chromatographically pure oil (280 mg, 84%) crystallized spontaneously, m.p. 61—65 °C (light petroleum). According to ^1H and ^{19}F NMR data, compound **3** consists of two diastereomers (1 : 1.2). ^1H NMR, δ: 1.43, 1.41 (both d, 3 H, Me, J = 6.0 Hz); 2.56—2.77 (m, 2 H, CH_2); 3.76, 3.83 (both s, 3 H, CO_2Me); 3.86 (s, 3 H, OMe); 3.87 (s, 3 H, OMe); 4.17, 4.26 (both m, 1 H, CH); 6.61 (s, 1 H, $H(5)_{Ar}$); 7.08, 7.09 (both s, 1 H, $H(8)_{Ar}$). ^{19}F NMR, δ: −1.11, −4.40 (both s, 3 F, CF_3). MS, m/z (I_{rel} (%)): 334 $[M]^+$ (19), 275 (100), 265 (8), 227 (77), 206 (20), 91 (21), 69 (10), 59 (45), 43 (23). Found (%): C, 53.86; H, 5.06. $C_{15}H_{17}F_3O_5$. Calculated (%): C, 53.89; H, 5.13.

References

1. J. M. McCall, R. B. McCall, R. E. TenBrink, B. V. Kamdar, S. J. Humphrey, V. H. Sethy, D. W. Harris, C. Daenzer, *J. Med. Chem.*, 1982, **25**, 75.
2. M. Yamato, T. Ishikawa, S. Ishikawa, K. Hashigaki, *Chem. Pharm. Bull.*, 1983, **31**, 2952.
3. H. G. Cutler, G. Majetich, X. Tian, P. Spearing, *J. Agric. Food Chem.*, 1997, **45**, 1422.
4. M. P. DeNinno, R. Schoenleber, R. J. Perner, L. Lijewski, K. E. Asin, D. R. Britton, R. MacKenzie, J. W. Kebabian, *J. Med. Chem.*, 1991, **34**, 2561.
5. F. Gatta, D. Piazza, M. R. Giudice, M. Massotti, *Farmaco, Ed. Sci.*, 1985, **40**, 942.
6. German Pat. 614 461, *Fortschr. Teerfarbenfabr. Verw. Industriezweige*, 1933, **22**, 343.
7. N. Choukchou-Braham, B. Mostefa-Kara, N. Cheikh, M. A. Didi, *Synth. Commun.*, 2005, **35**, 169.
8. E. M. Mmutlane, J. P. Michael, I. R. Green, C. B. de Koning, *Org. Biomol. Chem.*, 2004, **2**, 2461.
9. M. F. Semmelback, A. Zask, *J. Am. Chem. Soc.*, 1983, **105**, 2034.
10. V. I. Dyachenko, A. F. Kolomiets, A. V. Fokin, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 528 [*Russ. Chem. Bull.* (*Engl. Transl.*), 1995, **44**, 511]; V. I. Dyachenko, A. F. Kolomiets, A. V. Fokin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1988, 2557 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.* (*Engl. Transl.*), 1988, **37**, 2306]; V. I. Dyachenko, A. F. Kolomiets, A. V. Fokin, *Zh. Org. Khim.*, 1987, **23**, 893 [*Russ. J. Org. Chem.* (*Engl. Transl.*), 1987, **23**, 808].
11. V. I. Dyachenko, A. F. Kolomiets, A. V. Fokin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1987, 1080 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.* (*Engl. Transl.*), 1987, **36**, 995].
12. I. L. Knunyants, V. V. Shokhina, V. V. Tyuleneva, *Dokl. Akad. Nauk SSSR*, 1966, **169**, 594 [*Dokl. Chem.* (*Engl. Transl.*), 1966, **169**, 722].
13. V. V. Semenov, V. V. Rusak, E. M. Chartov , M. I. Zaretskii, L. D. Konyushkin, S. I. Firgang, A. O. Chizhov, V. V. Elkin, N. N. Latin, V. M. Bonashek, O. N. Stas´eva, *Izv. Akad. Nauk, Ser. Khim.*, 2007, 2364 [*Russ. Chem. Bull., Int. Ed.*, 2007, **56**, 2448].

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