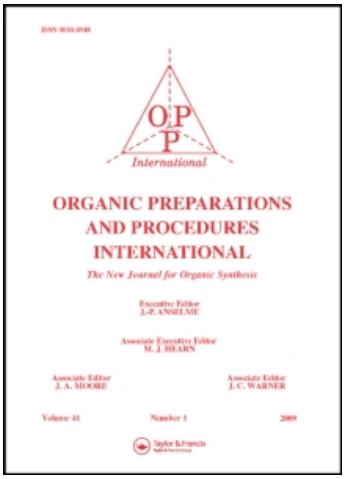


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

PREPARATION OF 3-(TRIFLUOROMEtHYL)COUMARINS

Wojciech Dmowski[a]; Krystyna Piasecka-Maciejewska[a]
[a] Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland

To cite this Article Dmowski, Wojciech and Piasecka-Maciejewska, Krystyna(2002) 'PREPARATION OF 3-(TRIFLUOROMEtHYL)COUMARINS', Organic Preparations and Procedures International, 34: 5, 514 — 517
To link to this Article: DOI: 10.1080/00304940209355771
URL: http://dx.doi.org/10.1080/00304940209355771

3. R. T. Jacobs, F. J. Brown, L. A. Cronk, D. Aharony, C. K. Buckner, E. J. Kusner, K. M. Kirkland and K. L. Neilson, *ibid.*, **36**, 394 (1993).

4. J. H. Jones, M. L. Jones, A. R. Moorman, H. Dumas, B. Flam, A. Sabetta, D. Sawicki, J. Sredy, B. Chevrier and A. Mitschler, *Abstracts of Papers of the 220 Meeting of the ACS*, 306-MEDI (2000).

5. V. J. Demopoulos and E. Rekka, *J. Pharm. Sci.*, **84**, 79 (1995).

6. D. Xia and D. M. Ketcha, *Org. Prep. Proced. Int.*, **27**, 503 (1995).

7. V. J. Demopoulos and I. Nicolaou, *Synthesis,* 1519 **(1998)**.

8. E. Vowinkel, *Chem. Ber.*, **99**, 1479 (1966).

9. E. Vowinkel, *ibid.*, **100,** 16 (1967).

10. J. G. Cannon and B. J. Demopoulos, *J. Heterocyclic Chem.*, **19,** 1195 (1982).

11. V. O. Illi, *Synthesis,* 387 **(1979)**.

12. T. Akiyama, H. Hirofuji, A. Hirose and S. Ozaki, *Synth. Commun.*, **24,** 2179 (1994).

13. G. M. Anatharamaiah and K. M. Sivanandaiah, *J. Chem. Soc. Perkin Trans. I,* 490 **(1977)**.

14. A. M. Felix, E. P. Heimer, T. L. Lambros, C. Tzougraki and J. Meienhofer, *J. Org. Chem.*, **21,** 4194 (1978).

****

PREPARATION OF 3-(TRIFLUOROMETHYL)COUMARINS

Submitted by (11/10/01)

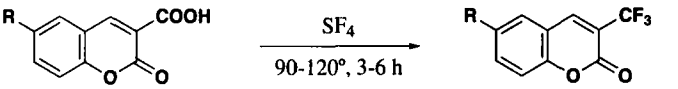
Wojciech Dmowski* and Krystyna Piasecka-Maciejewska

Institute of Organic Chemistry
Polish Academy of Sciences, 01-224 Warsaw, POLAND

Coumarins constitute an important class of naturally occurring compounds with useful pharmacological activity.[1,2] Numerous coumarins were used as steroid receptor modulators[3] and photopolymerization initiators[4]. Some attention has been paid to trifluoromethyl substituted coumarins as fluorescent markers for synthetic proteinases[5,6] and also as laser dyes.[7] Recently, a

number of coumarins, inclusive of fluorine containing ones, were patented as optical molecular sensors.[8] In all these applications only 4-trifluoromethyl substituted coumarins were used; they were synthesised by the zinc chloride catalysed condensation of phenols with 4,4,4-trifluoroacetoacetate (Pechmann reaction).[5,6] Enantioselective cathodic reduction of 4-(trifluoromethyl)coumarin with alkaloids as chiral catalysts was investigated; this resulted in 4-(trifluoromethyl)-3,4-dihydrocoumarin as the main product (28% yield and 8.4% ee).[9] A number of 3-perfluoroalkyl substituted coumarins were prepared by a sodium hydroxymethanesulfinate (Rongalite) initiated reactions of perfluoroalkyl iodides with coumarins[10] or by reactions of coumarins with perfluoroalkanesulphinates[11] in the presence of oxidants but no 3-(trifluoromethyl)coumarins were obtained by those methods. The only successful preparation of 3-trifluoromethyl substituted coumarins reported so far involves reactions of coumarins with bis(trifluoroacetyl) peroxide.[12]

It is well known that trifluoromethyl substituted heterocycles could be easily prepared by treatment of heterocyclic carboxylic acids with sulfur tetrafluoride.[13] In the present communication we report preparation of 3-(trifluoromethyl)coumarin (**2a**) and 3-(trifluoromethyl)-6-nitrocoumarin (**2b**) by treatment of the corresponding, commercially available, coumarin-3-carboxylic acids (**1a**) and (**1b**) with sulfur tetrafluoride.



1a, R = H
1b, R = NO_2

2a, R = H
2b, R = NO_2

The reactions require temperature within the range of 90-120° to proceed with satisfactory rate. Considerable amount of polymeric material was formed under such conditions, nevertheless, a column chromatography on silica gel allowed compounds **2** to be isolated with reasonable yields and of high purity.

The method is complementary to that utilizing bis(trifluoroacetyl) peroxide[12] and seems to be general and useful for the synthesis 3-(trifluoromethyl)coumarins from coumarin-3-carboxylic acids which are readily available by condensation of 2-hydroxybenzaldehydes with diethyl malonate.[14]

EXPERIMENTAL SECTION

Mps were determined in capillaries and are uncorrected. ^{1}H- and ^{19}F-NMR spectra were recorded in $CDCl_3$ with a Varian Gemini 200 spectrometer at 200 and 188 MHz, respectively; chemical shifts are in p.p.m. from internal TMS for protons and from internal $CFCl_3$ for fluorine nuclei (positive upfield). IR spectra were measured with a Perkin-Elmer Spectrum 2000 instrument.

General Procedure.- Coumarin-3-carboxylic acid **1a** or **1b** (1.90 or 2.35 g, 10 mmol) was placed in a 30 mL capacity stainless steel autoclave fitted with a needle valve, the autoclave was cooled in an

acetone-Dry Ice bath, evacuated, then sulfur tetrafluoride (*ca.* 10 g, 90 mmol) was condensed into it. The autoclave was agitated in a rocking furnace at 90° for 3 hrs (for **1a**) or at 120° for 6 hours (for **1b**). After completion of the reaction, gaseous products were let off (SF_4, SOF_2, HF) at RT and the yellow semisolid residue was dissolved in CH_2Cl_2 (50 mL). The solution was washed with aqueous $NaHCO_3$ then dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a yellow solid which was subjected to column chromatography on silica gel using a hexane-CH_2Cl_2 mixture (1:1) as the eluent to give compounds **2a** and **2b** as white crystalline substances.

3-(Trifluoromethyl)coumarin (2a): Yield 0.78 g (36%), mp. 122-123°. IR (CCl_4): 1764.7 cm^{-1} (vs, CO). ^1H NMR (200 MHz): δ 7.38 (m, 2H, arom.), 7.65 (m, 2H, arom.), 8.17 (s, 1H). ^{19}F NMR (188 MHz): δ 67.7 (s, CF_3).

Anal. Calcd for $C_{10}H_5F_3O_2$: C, 56.09; H, 2.35; F, 26.32. Found: C, 56.10; H, 2.32; F, 26.34

3-(Trifluoromethyl)-6-nitrocoumarin (2b): Yield 0.82 g (32%), mp. 184-185°. IR (CCl_4): 1777.1 cm^{-1} (vs, CO). ^1H NMR (200 MHz): δ 7.56 (d, $^3J_{HH}$ = 9.0 Hz, 1H, arom.), 8.26 (s, 1H), 8.56 (complex, 2H, arom). ^{19}F NMR (188 MHz): δ 67.0 (s, CF_3).

Anal. Calcd for $C_{10}H_4F_3NO_4$: C, 46.35; H, 1.56; F, 21.99; N, 5.41. Found: C, 46.30; H, 1.52; F, 22.00; N, 5.35

REFERENCES

1. L. Lazzeri Andeani and E. Lapi, *Boll .Chim. Farm.*, **99,** 583 (1960); *Chem. Abstr.,* **55**, 12668 (1961).
2. L. Bonsignore, G. Loy, D. Secci and A. Calignano, *Eur. J. Med. Chem.*, **28,** 517 (1993).
3. T. K. Jones, M. E. Goldman, Ch. L. F. Pooley, D. T. Winn, J. E. Edwards, S. J. West, Ch. M. Tegley, L. Zhi and L.G. Hamann, PCT Int.Appl. WO 96 19,458 (1994); *Chem. Abst.*, **125**, 142697 (1996).
4. N. Okuma, M. Takemochi, M. Miyagawa, H. Hayashi and T. Minami, Jpn. Kokai Tokkyo Koho JP 63,270,703 (1986); *Chem. Abst.*, **111**, 144206 (1989).
5. E .R. Bissel, A. R. Mitchell and R. E. Smith, *J. Org. Chem.*, **45,** 2283 (1980).
6. E. R. Bissel, D. K. Larson and M. C. Croudace, *J. Chem. Eng. Data*, **26,** 348 (1981).
7. A. N. Fletcher, *Appl. Phys.*, **14,** 295 (1977).
8. L. Makings and G. Zlokarnik, PCT Int.Appl. WO 00 35,900 (1994): *Chem. Abst.*, **133**, 421124 (2000).
9. N. Schoo and H. J. Schäfer, *Liebigs Ann. Chem.*, 601 (**1993**).
10. B. N. Huang, J. T. Liu and W. Y. Huang, *J. Chem .Soc. Perkin Trans. I*, 101 (**1994**).

11. J. T. Liu and W. Y. Huang, *J. Fluorine Chem.*, **95,** 131 (1999).

M. Matsui, K. Shibata, H. Muramatsu, H. Sawada and M. Nakayama, *Synlett,* 113 (**1991**); *Chem. Ber.,* **125**, 467 (1992).

13. For references see: W. Dmowski, *Introduction of Fluorine in Organic Compounds using Sulphur Tetrafluoride,* in B. Baasner, H. Hagemann, J.C. Tatlow (Ed.), *Houben-Weyl Methods in Organic Chemistry,* Vol. E10a, Georg Thieme Verlag, Stuttgart, New York, 1999, pp 321-405.

14. S. M. Lavagna, *J. Heterocyclic Chem.*, **32**, 573 (1995).

****

A SIMPLIFIED SYNTHESIS OF ETHYL 5-CHLORO-4-FLUORO-1*H*-INDOLE-2-CARBOXYLATE AND ETHYL 5-CHLORO-6-FLUORO-1*H*-INDOLE-2-CARBOXYLATE

Submitted by (12/03/01) Romano Silvestri*†, Gabriella De Martino† and Gianluca Sbardella††

† *Dipartimento di Studi Farmaceutici, Università di Roma "La Sapienza", Box 36 - Roma 62, P.le Aldo Moro 5, I-00185 Roma, ITALY*

†† *Dipartimento di Scienze Farmaceutiche, Università di Salerno, Via Ponte Don Melillo, I-84084 Fisciano (Salerno), ITALY*

Tel. +39 06 49913800; E-mail: romano.silvestri@uniroma1.it

During a search for novel anti-HIV-1 agents, we planned the synthesis of the indolyl aryl sulfones **7** and **8**, whose preparation required ethyl 5-chloro-6-fluoro-1*H*-indole-2-carboxylate (**5**) and ethyl 5-chloro-4-fluoro-1*H*-indole-2-carboxylate (**6**) as starting materials, respectively *(Fig. 1)*.[1]

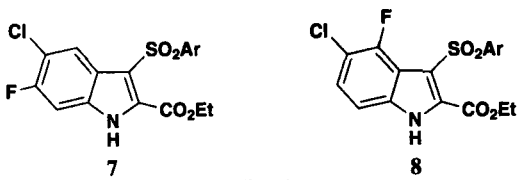


Fig. 1

Compounds **5** and **6** were obtained according to literature procedures[2,3] from commercially available 3-fluoroaniline in five steps *via* 4-chloro-3-fluoroaniline (**2**) as a key intermediate. This compound was obtained by hydrolysis of *N*-pivaloyl 4-chloro-3-fluoroaniline (**1**) prepared as reported[4] by chlorination of *N*-pivaloyl 3-fluoroaniline[5] with *N*-chlorosuccinimide. Coupling of the diazonium salt of 4-