

# A Convenient Preparation of 5-(trifluoromethyl)dipyrromethanes<sup>1</sup>

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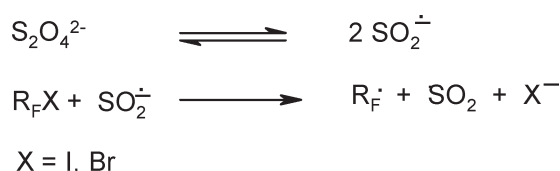
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Sodium dithionite initiated reactions of pyrrole and 1-methylpyrrole with 1-bromo-1-chloro-2,2,2-trifluoroethane in an acetonitrile-water solution provide the respective 5-(trifluoromethyl)dipyrromethanes (**1**) and (**3**) as main products in 40 – 58 % isolated yields and of high purity. Small amounts of tripyrranes (**2**) and (**4**) are also formed and could be isolated from the reaction mixtures.

Keywords: 5-(Trifluoromethyl)dipyrromethanes, pyrroles, 1-bromo-1-chloro-2,2,2-trifluoroethane, sodium dithionite

5-(Perfluoroalkyl)dipyrromethanes are key intermediates in the synthesis of electron deficient porphyrins substituted with perfluoroalkyl groups located at the *meso* positions.<sup>1,2</sup> General method of the synthesis of these intermediates consists of the acid catalysed condensation of pyrrole with perfluoroalkyl aldehydes. The most important one, 5-(trifluoromethyl)dipyrromethane (**1**) was prepared in a 35 – 50 % yield by reacting pyrrole with trifluoroacetaldehyde methyl hemiacetal<sup>2</sup> or with trifluoroacetaldehyde hydride.<sup>3</sup> The main disadvantage of those syntheses is high cost of trifluoroacetaldehyde and its derivatives.

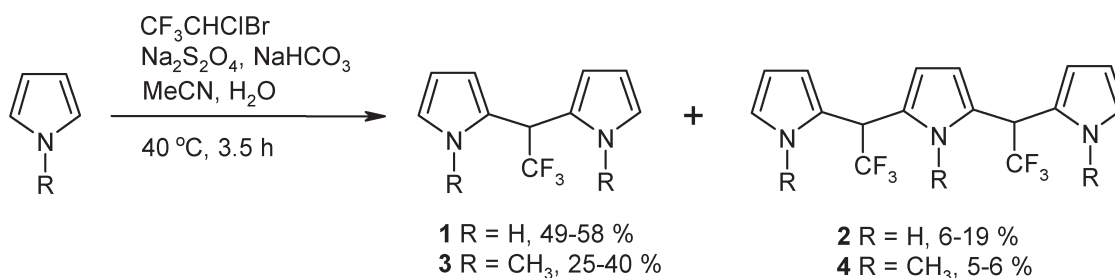
In this paper we report very simple and inexpensive synthesis of 5-(trifluoro-methyl)dipyrromethane (**1**) and its N-methyl substituted analogue (**3**) via a sodium dithionite initiated condensation of pyrrole and 1-methylpyrrole with 1-bromo-1-chloro-2,2,2-trifluoroethane (Halothane<sup>®</sup>). Our method has been based on the procedure, developed by W. Y. Huang et al.<sup>4,5</sup> and known as “sulphinatodehalogenation”, which provides an easy way of generating perfluoroalkyl radicals from perfluoroalkyl halides in aqueous solutions using sodium dithionite or related compounds as the free radical initiators. In this reaction system, dithionite anions ( $S_2O_4^{2-}$ ) exist in an equilibrium with radical anions  $SO_2^{\dot{-}}$ , which by a SET process abstract halogens from  $R_F X$  molecules to generate perfluoroalkyl radicals (Scheme 1).



Scheme 1

Generated, electron deficient perfluoroalkyl alkyl radicals could be effectively trapped by electron rich substrates like alkenes, alkynes, arenes, and heteroarenes to give addition or substitution products. Thus, in reactions with pyrrole and 1-methylpyrrole the respective 2-(perfluoroalkyl)pyrroles were obtained in 65–68 % yields.<sup>6,7</sup>

We reported previously that sulfinatodehalogenation procedure could be applied to 1-bromo-1-chloro-2,2,2-trifluoroethane, commercially available as Halothane<sup>®</sup> (inhalation anaesthetic), to generate  $CF_3CHCl^{\dot{}}$  radicals which readily reacted with enol ethers such as 2-methoxypropene, ethyl vinyl ether and enol ethers of cyclic ketones to give addition products.<sup>8,9</sup> Presently, we have found that the  $CF_3CHCl^{\dot{}}$  radicals react in quite unusual way with pyrroles; instead of the expected  $CF_3CHCl$ -substituted pyrroles, products in which the pyrrole rings are coupled via a



Scheme 2

$CF_3CH=$  bridge, were formed. 5-(trifluoromethyl)dipyrromethanes **1** and **3** were the main products together with small amounts of tripyrranes **2** and **4** (Scheme 2). High

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temperature mass spectra (to 240 °C) of the crude reaction products revealed also the presence of trace amounts of higher homologues, containing up to seven pyrrole rings, but no cyclic porphyrinogen like compounds were detected.

The reactions were carried out under, generally, typical conditions in an acetonitrile-water solution (2 : 1) using  $\text{Na}_2\text{S}_2\text{O}_4$  as a free radical initiator and  $\text{NaHCO}_3$  as a buffer. The ratio of "dimeric" compounds **1** and **3** to "trimeric" compounds **2** and **4** depended, to some extent, on the ratio of pyrroles to  $\text{CF}_3\text{CHClBr}$ , but dipyrromethanes **1** and **3** were always the major products. The highest yields of **1** and **3** were obtained using 3 moles of pyrrole per 1 mole of  $\text{CF}_3\text{CHClBr}$ ; decrease in the amount of pyrrole resulted in not only lower yields of **1** and **3**, but also in lower total yields.

We have found that the important factor is the amount of the initiator used. In most of the published works, inclusive ours,<sup>8,9</sup>  $\text{Na}_2\text{S}_2\text{O}_4$  and perhaloalkane were used in equimolar amounts. However, in the present case the best results were obtained with only 0.25 equivalent of  $\text{Na}_2\text{S}_2\text{O}_4$ . The reactions proceeded at the same rate affording similar yields of products, like with equivalent amount of the initiator but less polymeric tar, was formed and the crude products were much cleaner. Low ratio of the initiator to  $\text{CF}_3\text{CHClBr}$  suggests a free radical chain mechanism, possibly as depicted in Scheme 3.

Compounds **1** and **2** were isolated from the crude reaction mixture by column chromatography or, alternatively, dipyrromethane (**1**) was isolated (and purified) by double distillation in vacuum; the latter method seems to be more convenient for larger scale preparation of **1**. *N*-methyl substituted compounds **3** and **4** were easily separated each from the other due to their drastically different solubility in methanol. Elemental analyses gave unequivocal evidence that molecules of compounds **1** and **3** consist of two pyrrole rings and one  $\text{CF}_3$  group, while compounds **2** and **4** should be composed of three pyrrole rings and two  $\text{CF}_3$  groups. The simplicity of the NMR spectra of compounds **1** – **4** implied their highly symmetric structure. The  $^1\text{H}$  NMR

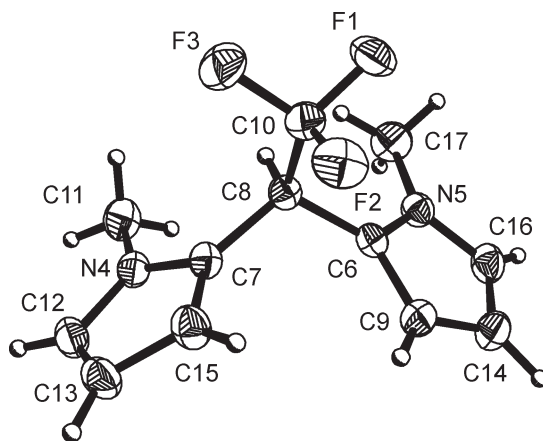
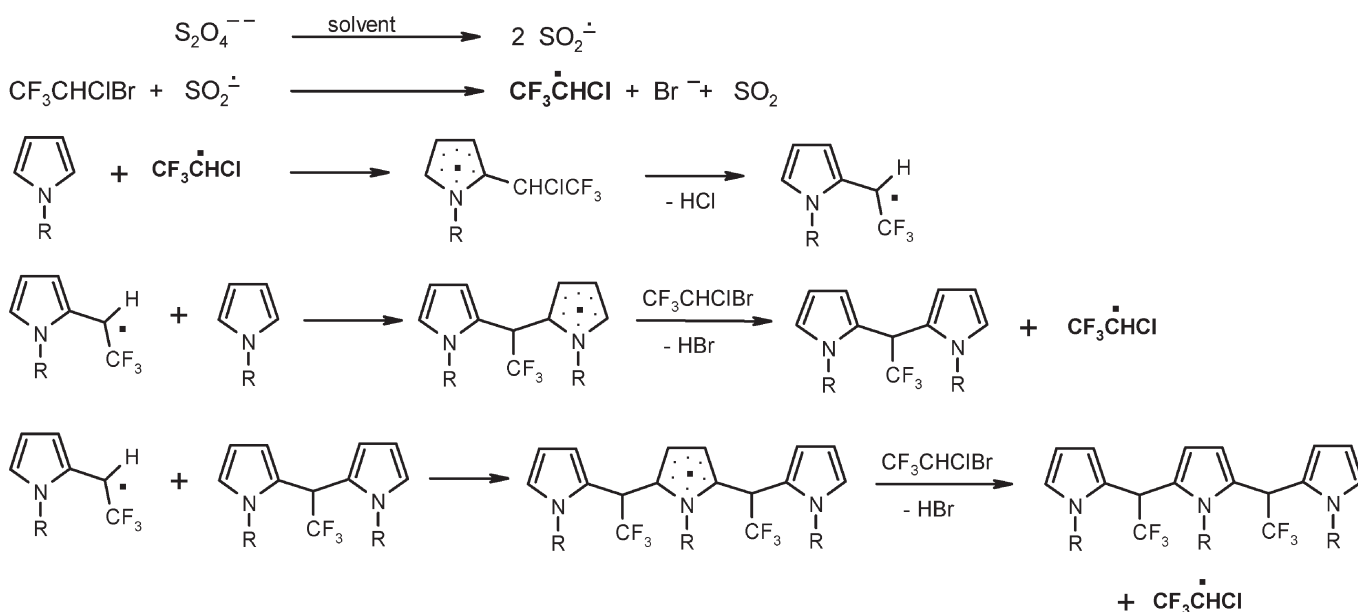


Fig. 1 – X-ray crystal structure for **3** with crystallographic atoms numbering

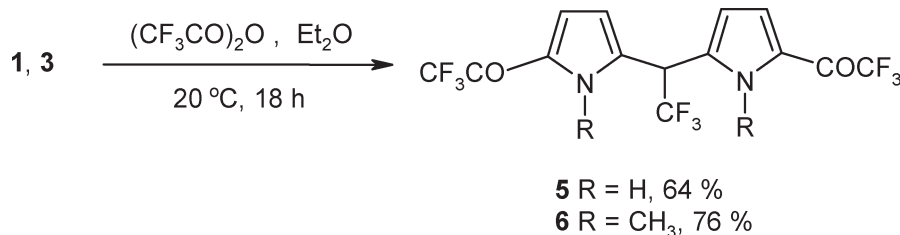
spectrum of **1** is consisted with the reported one<sup>2</sup> but we achieved better resolution. Dipyrromethane **3** forms large well-shaped crystals, structure of which was proved by X-ray analysis (Fig. 1). Interestingly, compound **3** was found to be a rigid molecule in which the two pyrrole ring planes form a dihedral angle of 61 (1)° degree.

Dipyrromethanes **1** and **3** have proven to be stable molecules and could be stored in the dark for long time. The reactivity of the pyrrole rings in both **1** and **3** was found to be somewhat reduced as compared with the original pyrroles; thus, treatment with trifluoroacetyl anhydride at ambient temperature afforded 1,9-bis(trifluoroacetyl) derivatives **5** and **6**, respectively in 64 and 76 % yields (Scheme 4) but the attempted Vilsmeier-Haack acetylation<sup>10</sup> with *N,N*-diethylacetamide and  $\text{POCl}_3$  resulted in undefined oils.

In summary, the title reactions represent a novel and simple approach to 5-(trifluoromethyl)dipyrromethanes. Our synthesis of **1** is complementary to the reported ones<sup>2,3</sup> but is more convenient and much less expensive. Compound **3** and tripyrranes **2** and **4** were obtained for the first



Scheme 3



Scheme 4

time. The described reactions seems to be unique; the attempted reactions of  $\text{CF}_3\text{CHClBr}$  with other heteroaromatics failed; with imidazol, pyridine and pyridazine no reaction occurred but with furan undefined oil was formed.

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### SAŽETAK

#### Prikladna priprava 5-(trifluormetil)dipirometana

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Reakcije pirola i 1-metilpirola s 1-brom-1-klor-2,2,2-trifluoetanom u vodenom acetonitrilu potaknute natrijevim ditionitom, kao glavne produkte daju 5-(trifluormetil)dipirometane (**1**) i (**3**) uz 40–58 postotni prinos i veliku čistoću. U reakcijskoj smjesi dodatno su nastale i izolirane male količine tripirana (**2**) i (**4**).

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