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Regioselective Synthesis of 3-Substituted Pyrroles by Nucleophilic Addition of 3-(1-Arylsulfonylalkyl) Pyrroles Activated under Basic or Acid Conditions

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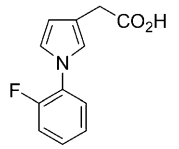
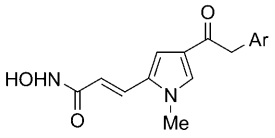
This paper is dedicated to Prof. Alfredo Ricci on the occasion of his retirement

Functionalization of heteroaromatic systems in a regioselective fashion often represents a considerable challenge. The insertion of a desired substituent at a specific position is in fact thwarted by the intrinsic reactivity of the ring. Electron-rich five-membered-ring heterocycles are preferentially attacked at C2 by electrophiles leading to the corresponding substituted derivatives.[1] Even metalation by strongly basic organometallic reagents occurs at the same position providing an electronically complementary way of functionalization without altering the regioselectivity bias. In this context, pyrrole rings exhibit the usual trend towards a preferential C2 substitution, whereas it is widely known that indoles have a tendency to afford 3-substituted derivatives.[2] The interest in 3-functionalized pyrroles mainly stems from their embedding in several compounds of natural as well as synthetic origin, many of which display very interesting biological activities.[3] In addition, polymers and other organic materials often include the 3-alkylpyrrole moiety as a key structural motif.[4]

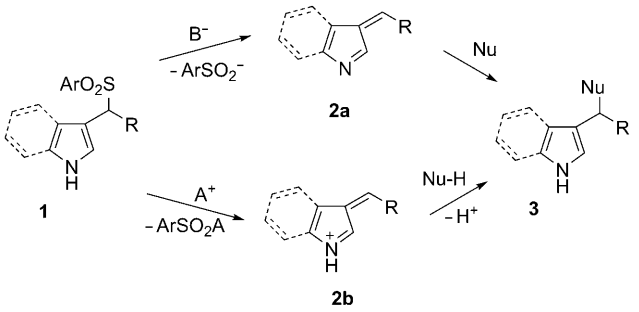


Anti-inflammatory activity



HDAC inhibitors

It has been reported that N-substitution in pyrroles has a significant effect in the orientation of the incoming electrophile during the corresponding aromatic substitution.[5] Increasing the bulkiness of the N-substituent, regardless of its electronic properties, usually tends to shift the regioselectivity towards the 3-position.[6] The most pronounced shift is reported using the *N*-triisopropylsilyl group. This moiety has the considerable advantage to be easily introduced in the pyrrole ring, but also to be very easily removed under mild conditions.[7] On the other hand, *N*-alkyl pyrroles have recently been involved in an interesting synthetic approach directed to the preparation of 3-substituted pyrroles using alkynes, as well as carbonyl derivatives, under indium catalysis.[8] Because of the involvement of bispyrrolyl intermediates in the reaction pathway, a threefold to fourfold excess of pyrrole substrates had to be used to ensure an efficient conversion. Recently, we reported an innovative procedure for the preparation of 3-substituted indole derivatives **3** based on the utilization of 3-(1-arylsulfonylalkyl) indoles **1** as precursors of reactive alkylideneindolenines **2a** (Scheme 1).[9]



Scheme 1. General synthetic strategy for indole or pyrrole functionalization. Ar = aryl; Nu = nucleophile.

Upon removal of arylsulfinic acid under basic conditions, sulfonyl indole **1** is converted into **2a**, which effectively acts as a vinylogous imino derivative in the reaction with a wide range of nucleophilic reagents.[10] Acidic reagents (Lewis-type) are also able to remove the arylsulfinic group from **1** leaving an iminium ion **2b**, which can react with weak nucleophiles thus generating the substituted products **3**.[11] An iminium ion structurally related to **2b** is supposed to be active in the indium-catalyzed procedure involving reaction of *N*-alkyl pyrroles.[8] Therefore, we decided to test the feasibility of our procedure effective on indoles for the preparation of sulfonyl pyrrole analogues.[12] Amongst the various N-substituted pyrroles tested for this purpose, commercial *N*-triisopropylsilyl pyrrole **4** proved to be the most effective in giving the corresponding sulfonyl pyrroles **5** (Table 1).[13]

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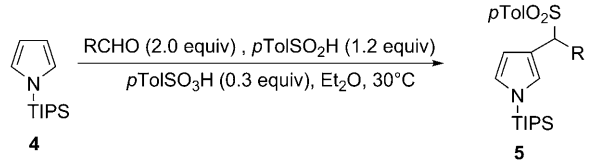
Table 1. Synthesis of 1-triisopropylsilyl-3-(1-tosylalkyl) pyrroles **5** by a three-component reaction. TIPS = triisopropylsilyl.

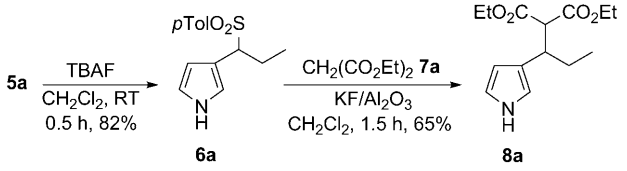


Entry	Product	R	Yield [%][a]
1	**5a**	Et	77
2	**5b**	n-C_5H_{11}	69
3	**5c**	n-$C_3H_7CH{=}CH_2$	75
4	**5d**	CH_2CH_2Ph	58
5	**5e**	c-C_6H_{11}	78
6	**5f**	C_6H_5	55
7	**5g**	4-tBuC_6H_4	60
8	**5h**	4-$NO_2C_6H_4$	57
9	**5i**	4-$MeOC_6H_4$	64
10	**5j**	4-PhC_6H_4	56

[a] Yield of pure isolated product.

The triisopropylsilyl (TIPS) moiety was of crucial importance for the subsequent synthetic application of sulfonyl pyrroles **5**, as described later in this communication. A set of aryl- as well as alkyl aldehydes, were found to be effective in producing the corresponding sulfonyl pyrroles **5**. Because of the known sensitivity of the pyrrole ring towards acidic environment, the experimental conditions had to be carefully tuned. Relative to the original procedure optimized for indoles, a decrease in the medium acidity of *para*-toluenesulfonic acid and an increase of the amount of the aldehyde were mandatory to obtain satisfactory yields. Sulfonyl pyrroles **5** have been subsequently tested in the reaction with different active methylene compounds under basic conditions. However, as already observed for the parent indole derivatives, N-protected compounds **5** did not eliminate the arylsulfinic moiety in the presence of a base. Formation of the reactive alkylideneindolenine intermediate related to **2a** was not observed. It was thus necessary to remove the TIPS group prior to the nucleophile addition using tetrabutylammonium fluoride (TBAF) under standard conditions (Scheme 2). The unsubstituted compound **6a**, resulting from deprotection of **5a**, reacted as expected with diethyl malonate **7a** in the presence of KF on basic alumina, leading to the functionalized adduct **8a**.

The modest results recorded in the described two-step process, prompted us to exploit an alternative procedure to obtain adducts of type **8**. A preliminary observation made



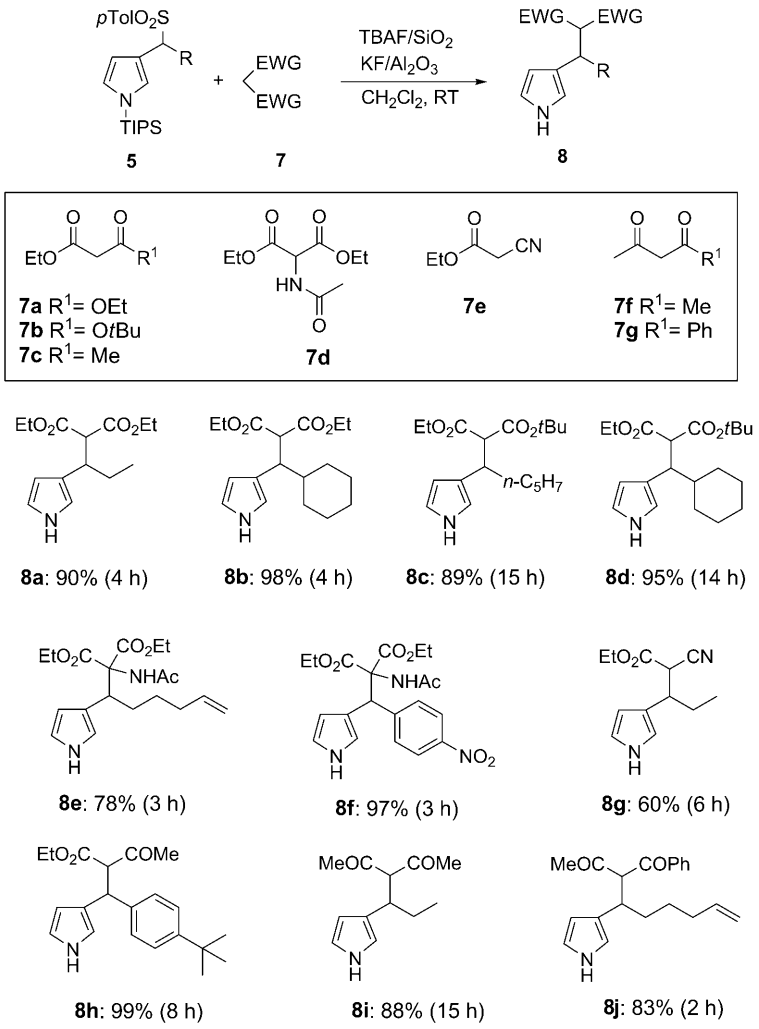
Scheme 2. Two-step synthesis of functionalized 3-substituted pyrroles **8**. *p*Tol = *p*-tolyl.

during the desilylation of compound **5a** was that the fluoride anion was unable to achieve eliminative desulfonylation to give intermediate **2a** in the presence of diethyl malonate **7a**. Potassium fluoride on basic alumina acted apparently as a basic promoter, being ineffective in aiding the desilylation of compounds **5**.[14] Organic reactions on a solid support represent a crucial feature for the development of environmentally friendly chemical processes. According to this principle, a procedure involving a fully heterogeneous system for conversion of derivatives **5** to functionalized pyrroles **8** was envisaged.[15] Silica-gel-supported TBAF[16] was demonstrated to be effective for desilylation of derivatives **5** and therefore synthesis of compounds **8** was attempted by simply mixing sulfonyl pyrroles **5** and two solid promoters (TBAF/SiO_2 and KF/basic Al_2O_3) in the presence of diethyl malonate **7a** (Scheme 3). To our delight, the two solid promoters worked independently in a domino process. As soon as desilylated pyrrole **6** was formed it reacted with the nucleophile through the alkylidenepyrroline intermediate **2a** leading to the final functionalized pyrrole **8** (Scheme 3).

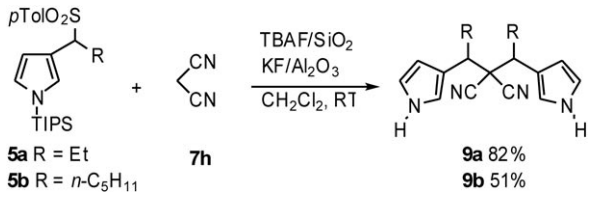
The chemical yields for this process were far superior compared to the two-step transformation as demonstrated for the preparation of compound **8a** (53 vs. 90% as reported in Scheme 3). A large variety of methylene active reagents **7** were then reacted with sulfonyl pyrroles **5**. Malonic acid diesters, 1,3-dicarbonyl derivatives, and β-keto esters were equally effective in giving 3-functionalized pyrroles **8** in excellent yields (Scheme 3). In particular, 2-acetamido malonate **7d** was able to provide a rapid entry to pyrroles **8e** and **8f** (Scheme 3), which can be considered as precursors of the corresponding amino acid derivatives achievable by a common hydrolysis–decarboxylation procedure. A particular behavior was observed using malononitrile **7h**, which in the reaction with sulfonyl pyrroles **5a** and **5b** afforded compounds **9** deriving from a double attack (Scheme 4). This result is consistent with the low steric hindrance of the malononitrile enolate, which allows multiple addition to occur.[17]

Prior removal of the *N*-TIPS group from sulfonyl pyrroles **5** is required for every process carried out under basic conditions. Conversely, generation of reactive iminium ions of type **2b** using Lewis acid promoters, may be done in the presence of the N-protection, which often even facilitates its formation.[8] Using $AlEtCl_2$, a fast elimination of the arylsulfonyl anion on the sulfonyl pyrroles **5** was indeed observed at moderately low temperature (−10 °C). The resulting iminium ion intermediate promptly reacted with a series of nucleophilic reagents **10** leading to the corresponding adducts **11** (Scheme 5).

Silyl enol ethers and silyl ketene acetals **10a–f** were effective in giving the corresponding adducts in good yields (Scheme 5). Particularly, the utilization of silyl derivatives **10e** and **10f** gave a ready entry to pyrrole derivatives **11g** and **11h**, which are hard to access through a conventional Friedel–Crafts process. Similarly, a densely functionalized pyrrole derivative **11i** was prepared by reaction of sulfonyl pyrrole **5a** with 2-trimethylsilyloxy furan **10g** (Scheme 5).



Scheme 3. Reaction of sulfonyl pyrroles **5** with methylene active compounds leading to 3-functionalized pyrrole derivatives **8**. Reaction conditions: sulfonyl pyrrole **5** (1.0 mmol), nucleophile **7** (1.5 mmol), tetrabutylammonium fluoride (TBAF)/SiO_2 (1.2 g), and KF/Al_2O_3 (2.5 g) in dichloromethane (10 mL) at RT. Reaction times are in parentheses. Product yields of compounds **8** are that of the pure isolated product.



Scheme 4. Synthesis of bis-adducts **9** using manolonitrile as the nucleophile.

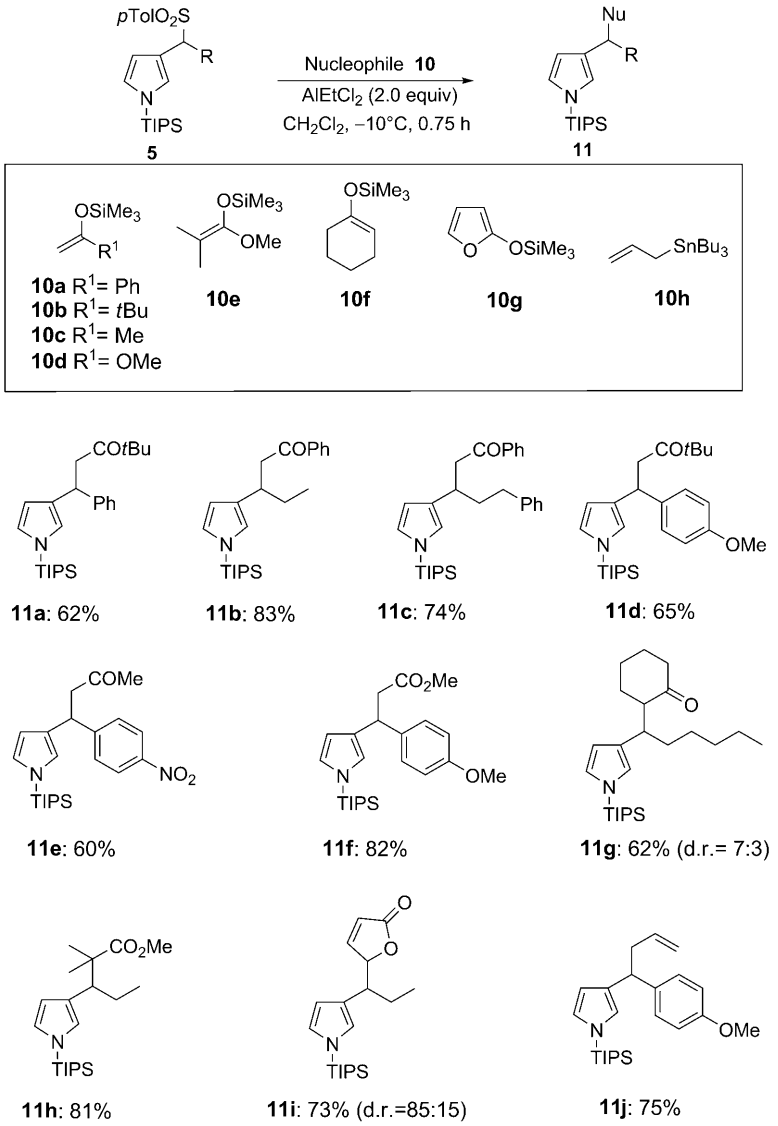
Introduction of an allyl framework by electrophilic substitution is a common practice in synthesis because of the manifold transformations pertaining to terminal double bonds. Using our reaction conditions, allyltrimethylsilane was poorly effective as an allylating agent, whereas better results were obtained using the more nucleophilic allyltributyltin **10h**, as evidenced in the formation of compound **11j** (Scheme 5). Interestingly, in all the reactions tested using $AlEtCl_2$, the Lewis acid did not affect the *N*-TIPS protection and so it was therefore retained in the final functionalized pyrroles **11**. This feature increases the versatility of our procedure because unlike *N*-alkyl pyrroles, the silyl protecting group can be easily removed under mild conditions.[18]

In conclusion, a viable and regioselective synthesis of 3-(1-arylsulfonylalkyl) pyrroles **5** can be carried out starting from commercially available *N*-TIPS pyrrole **4**. These sulfonyl pyrrole derivatives undergo N-deprotection, sulfinic acid elimination, and nucleophilic addition by methylene-active compounds **7** by using a mixture of solid promoters (TBAF/SiO_2 and KF/Al_2O_3). In a complementary way, removal of the arylsulfinate anion from sulfonyl pyrroles **5** by $AlEtCl_2$ generates the iminium species **2b**, which reacts with silyl enol ethers and related weak nucleophiles **10** to provide a different set of functionalized pyrroles **11**. These results demonstrate that this new procedure provides a viable access to 3-functionalized pyrroles, which are often otherwise difficult to produce. Applications in asymmetric synthesis can be foreseen.

Experimental Section

General procedure for the synthesis of compounds 5: The appropriate aldehyde (4 mmol) was added to a stirred solution of pyrrole **4** (2 mmol), monohydrate *para*-toluenesulfonic acid (0.6 mmol), and *para*-toluenesulfinic acid (2.4 mmol) in Et_2O (1.5 mL). The resulting reaction mixture was stirred at 30 °C for 2 h and, after cooling, was treated with saturated $NaHCO_3$ (7 mL). The aqueous layer was extracted with CH_2Cl_2 (3× 20 mL) and the combined organic extracts were dried over Na_2SO_4. After filtration and removal of the solvent at reduced pressure, the obtained crude product **5** was purified by flash chromatography (hexane/ethyl acetate 8:2).

General procedure for the synthesis of compounds 8: TBAF on silica (1.2 mmol, 1.2 g) and KF on basic alumina (14 mmol, 2.5 g) were added to a stirred solution of sulfonyl pyrrole **5** (1 mmol) and active methylene compound **7** in CH_2Cl_2 (10 mL). The resulting heterogeneous mixture was stirred at room temperature for the appropriate time (see Scheme 3), then the solvent was removed at reduced pressure and the resulting solid mixture was directly charged into a flash chromatography column (hexane/ethyl acetate, 8:2), giving pure product **8**.



Scheme 5. Reaction of sulfonyl pyrroles **5** with silyl enol ethers and related nucleophiles in the presence of $AlEtCl_2$. Reaction conditions: sulfonyl pyrrole **5** (1.0 mmol), nucleophile **10** (1.5 mmol), and $AlEtCl_2$ (2.0 mmol) in dichloromethane (10 mL) at −10°C for 0.75 h. Product yields of compound **11** are that of the pure isolated product.

General procedure for the synthesis of compounds 11: The nucleophile **10** (1.5 mmol) and $AlEtCl_2$ (2 mmol) were added to a stirred solution of the sulfonyl pyrrole **5** (1 mmol) in dry CH_2Cl_2 (12 mL) and kept under nitrogen atmosphere at −10°C. After 0.75 h saturated NH_4Cl (12 mL) was added to the reaction mixture and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The organic phase was dried over Na_2SO_4 and after evaporation of the solvent under reduced pressure, the crude product **11** was purified by flash chromatography (hexane/ethyl acetate 95:5).

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Keywords: carbonyl compounds · heterocycles · imino compounds · nucleophilic addition · pyrroles

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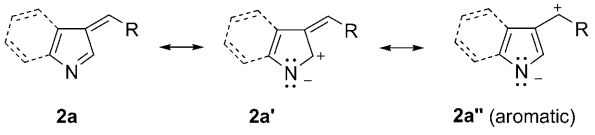

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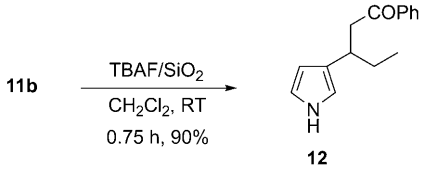
[18] As a representative example, cleavage of compound **11b** can be efficiently carried out using TBAF/SiO_2 leading to pyrrole **12** (see the Supporting Information for details).



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