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Regioselective addition of pyrrole to *N*-tosyl imines in the presence of $Cu(OTf)_2$

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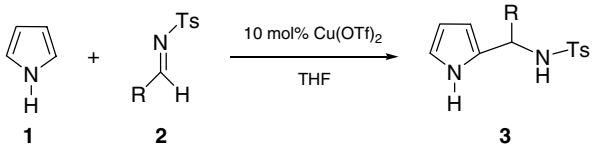
Abstract—The $Cu(OTf)_2$ catalysed reaction of pyrrole with *N*-tosyl imines gives pyrrole sulfonamides in high yields. The addition reaction takes place regioselectively at C(2) of the pyrrole. The procedure is simple and does not require anhydrous conditions.

Pyrroles are important because they can serve as intermediates for the synthesis of drugs, pigments and pharmaceuticals.[1] They can also be used as synthons for the synthesis of many natural and unnatural compounds.[2] The most common method for C-aminoalkylation of pyrroles is the reaction of formaldehyde with an amine hydrochloride, a process known as the Mannich reaction. This method is useful when secondary amines are used but there are some side products and low yield problems with primary amines.[3] The other method involves reactions of pyrrole compounds with imines that are activated by protonation using acids or by complexation with Lewis acids. It is known that acid catalysed reactions of pyrroles are limited because of their sensitivity to acids. The reactions of nitrogen-containing compounds activated with a catalytic amount of conventional Lewis acids are also limited due to their deactivation by strong coordination to the Lewis acid, in many cases stoichiometric amounts of the acid are required.[4] In order to obtain aminoalkylated pyrrole derivatives we focused on the addition reactions of pyrroles to *N*-tosyl imines, using metal triflates as the Lewis acid. These are also efficient catalysts for the synthesis of nitrogen-containing compounds due to their high activity towards imines.[5] We have recently reported the metal triflate catalysed conjugate addition of homochiral pyrroles to α,β-unsaturated esters in good yields and showed that metal triflates are very suitable Lewis acids for the derivatisation of pyrrole compounds.[6]



1 2 3

Scheme 1.

In this work, we describe the regioselective copper triflate catalysed addition of pyrrole to tosyl imines (Scheme 1). *N*-Tosyl imines were obtained in high yields by the reaction of *p*-toluenesulfonamide and aldehydes in the presence of *p*-toluenesulfonic acid.

The addition reaction of pyrrole **1** to *N*-benzylidene-4-methylbenzenesulfonamide **2a** was performed in THF at −20, 0 °C and rt with different metal triflates (Table 1). The addition product **3a** was formed in 47% yield at 0 °C only with $Cu(OTf)_2$. All the other metal triflates catalysed the addition reaction at rt but only with low yields (5–40%) and no addition product was observed at −20 °C.

Of various organic solvents, CH_3CN, acetone, THF, Et_2O, DCM and toluene, in the presence of 10 mol % $Cu(OTf)_2$ at 0 °C, the best chemical yield (47%) was obtained in THF.

The reactions of pyrrole with other tosyl imines were now carried out using the 10 mol % $Cu(OTf)_2$ in THF system at 0 °C and rt. Pyrroles **3a**–**g** were obtained in higher yields at 0 °C (Table 2) than at rt. Tosyl imines with electron-withdrawing groups (Table 2, entries 5 and 7) gave addition products in higher yields than those

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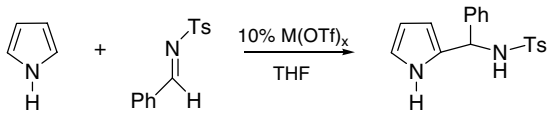
Table 1. The reactions of pyrrole with **2a** at different temperatures with different metal triflates[a]



1 **2a** **3a**

Entry	Catalyst	0 °C Yield(%)[b]	rt Yield(%)[b]
1	$Cu(OTf)_2$	47	40
2	$Zn(OTf)_2$	—	20
3	$La(OTf)_3$	—	15
4	$Nd(OTf)_3$	—	12
5	$Ga(OTf)_3$	—	5
6	$Yb(OTf)_3$	—	10
7	$Y(OTf)_3$	—	30

[a] Reaction conditions: $M(OTf)_x$ (10 mol %), pyrrole (1 equiv) and **2a** (1 equiv); THF; 6 h.
[b] Yield refers to pure product after column chromatography.

Table 2. $Cu(OTf)_2$catalysed reactions of pyrrole with 2 equiv of *N*-tosyl imines[a]

Entry	R	0 °C, Yield (%)[b]	rt Yield (%)[b]	Product
1	C_6H_5	47	40	**3a**
2	4-CH_3O–C_6H_4	64	52	**3b**
3	2-CH_3O–C_6H_4	65	65	**3c**
4	4-CH_3–C_6H_4	52	44	**3d**
5	4-NO_2–C_6H_4	85	72	**3e**
6	4-F–C_6H_4	70	58	**3f**
7	4-CF_3–C_6H_4	82	71	**3g**

[a] Reaction conditions: $Cu(OTf)_2$ (10 mol %), pyrrole (1 equiv) and *N*-tosyl imine (1 equiv); THF; 6 h.
[b] Yield refers to pure product after column chromatography.

with electron-donating groups. The reaction occurred regioselectively at C(2) of the pyrrole. The position of the substituent was assigned on the basis of ^1H NMR and COSY spectra and also by comparison with known 2-alkylated pyrroles.[7]

Using 2 equiv of pyrrole at 0 °C and rt, *meso*-substituted dipyrromethane derivatives were obtained as side products in some reactions (Table 3, **4a**–**d**). These are important intermediates for the synthesis of porphyrins, chlorins, corroles, corrins, porphyrinogens and related structures.[8] The *meso*-substituted dipyrromethanes were separated by flash column chromatography and identified by ^{13}C NMR and ^1H NMR techniques. All spectroscopic data for compounds **4a**–**d** were in agreement with published data.[9] The synthesis of dipyrromethanes as the main products using *N*-tosyl imines is under investigation.

The addition reactions of pyrrole to tosyl imines occur regioselectively at C(2) of the pyrrole. 3-Substituted or *N*-substituted pyrrole side products were not observed in any of the reactions. That anhydrous conditions are not required is another advantage.

In conclusion, we have described a novel method for the regioselective derivatisation of pyrroles with *N*-tosyl imines using $Cu(OTf)_2$ as the Lewis acid catalyst. The new pyrrole derivatives were synthesised in high yields by a simple reaction procedure.

Acknowledgement

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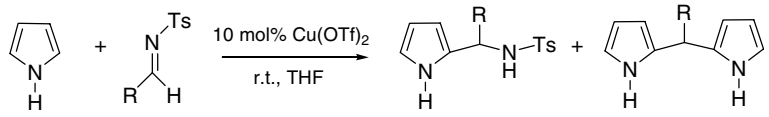
Table 3. $Cu(OTf)_2$ catalysed addition reactions of pyrrole to *N*-tosyl imine with 2 equiv of pyrrole at rt[a]



1 **2** **3a-g** **4a-d**

Entry	R	**3a**–**g** Yield (%)[b]	**4a**–**d** Yield (%)[b]	Side product
1	C_6H_5	55	20	**4a**
2	4-CH_3O–C_6H_4	53	18	**4b**
3	2-CH_3O–C_6H_4	70	—	
4	4-CH_3–C_6H_4	44	25	**4c**
5	4-NO_2–C_6H_4	80	—	
6	4-F–C_6H_4	63	15	**4d**
7	4-CF_3–C_6H_4	74	—	

[a] Reaction conditions: $Cu(OTf)_2$ (10 mol %), pyrrole (1 equiv) and *N*-tosyl imine (2 equiv); THF; 6 h.
[b] Yield refers to pure product after column chromatography.

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7. (a) Experimental procedure for the synthesis of **3a**: A mixture of *N*-benzylidene-4-methylbenzenesulfonamide **2a** (1 mmol) and $Cu(OTf)_2$ (0.1 mmol) was stirred in 10 mL THF for 30 min. Next, a solution of pyrrole (1 mmol) in 5 mL THF was added dropwise. The reaction was monitored by TLC and the reaction was complete in 6 h. The mixture was passed through a short column packed with silica gel eluting with ethyl acetate to remove the $Cu(OTf)_2$. The eluent was evaporated under reduced pressure and the crude product was purified by flash column chromatography over silica gel 60 (230–400 mesh, ethyl acetate/hexane, 1:3). Selected data for **3a**: Pale yellow viscous oil; R_f: 0.40 (1:3 EtOAc/hexane); IR (KBr) 3458, 2085, 1633, 1390, 1282, 1136, 1080, 1021, 689, 605, 531 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.38 (s, 3H, CH_3), 5.57–5.60 (m, 2H, C3-H, CH), 5.84 (br s, 1H, SO_2NH), 5.97 (br s, 1H, C4-H), 6.66 (br s, 1H, C5-H), 7.11–7.20 (m, 7H, Ar–H), 7.53 (d, $J = 8.4$, 2H, Ar–H), 8.76 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.49, 55.78, 108.20, 118.57, 127.16, 127.38, 127.57, 128.35, 129.05, 129.29, 130.53, 137.47, 138.89, 142.87. Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58; S, 9.82. Found: C, 66.12; H, 5.63; N, 8.40; S, 9.73. Selected data for **3c**: light brown solid; mp: 132–133 °C; R_f: 0.34 (1:3 EtOAc/hexane); IR (KBr) 3440, 2954, 2835, 1638, 1491, 1453, 1328, 1247, 1156, 1092, 1023, 909, 790, 743, 664, 549 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.37 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 5.51 (br s, 1H, C3-H), 5.64 (d, $J = 9.3$, 1H, CH), 5.88 (d, $J = 9.3$, 1H, SO_2NH), 5.97 (br s, 1H, C4-H), 6.70 (br s, 1H, C5-H), 6.72–6.74 (m, 1H, Ar–H), 6.81–6.83 (m, 1H, Ar–H), 7.00–7.02 (m, 1H, Ar–H), 7.08 (d, $J = 8.2$, 2H, Ar–H), 7.16–7.19 (m, 1H, Ar–H), 7.55 (d, $J = 8.2$, 2H, Ar–H), 8.72 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.55, 53.85, 55.45, 107.04, 108.26, 111.21, 118.01, 120.87, 126.82, 127.22, 129.09, 129.60, 130.55, 137.86, 142.55, 156.76. Anal. Calcd for $C_{19}H_{20}N_2O_3S$: C, 64.02; H, 5.66; N, 7.86; S, 9.00. Found: C, 64.11; H, 5.81; N, 7.82; S, 8.75. For 2- and 3-alkylated pyrroles, see: (b) Kotsuki, H; Nishiuchi, M.; Kobayashi, S.; Nishizawa, H. *J. Org. Chem.* **1990**, *55*, 2969–2972; (c) Jorapur, Y. R.; Lee, C.-H.; Chi, D. Y. *Org. Lett.* **2005**, *7*, 1231–1234.
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