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Magnesiation Employing Grignard Reagents and Catalytic Amine. Application to the Functionalization of *N*-Phenylsulfonylpyrrole

Andrew Dinsmore,* David G. Billing, Karen Mandy, Joseph P. Michael, Daniel Mogano, and Shivaputra Patil

Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, PO Wits, 2050, South Africa

andy@aurum.wits.ac.za

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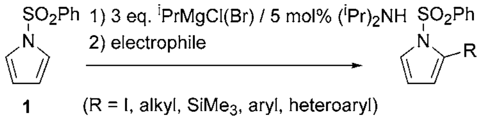
ABSTRACT



***N*-Phenylsulfonylpyrrole 1 is magnesiated by treatment with isopropylmagnesium chloride and catalytic diisopropylamine. Reaction with various electrophiles, including palladium-catalyzed aryl- and heteroaryl cross-coupling, provides 2-substituted phenylsulfonylpyrroles in moderate to good yields.**

N-Sulfonylpyrroles are more crystalline, less electron-rich, and hence easier to handle than the parent unprotected pyrroles. During an investigation of their application in natural product synthesis, we became interested in extending the magnesiation protocol of Kondo et al.[1] to *N*-phenylsulfonylpyrrole **1**. The original ortho magnesiation methodology had made use of Hauser or magnesium bis-amide bases and had been applied to *N*-phenylsulfonylindoles and thiophenes. Here we report the results of this study and show that the original methodology can be made *catalytic* with respect to the amine employed.

Previous studies have demonstrated that the reaction of *N*-phenylsulfonylpyrrole **1** with electrophiles requires Lewis acid activation. Under these conditions and in contrast to more bulky *N*-protecting groups, the sulfonyl-protected pyrroles generally give mixtures of 2- and 3-substituted products,[2] though selectivity for the 2- or 3-position can be achieved by careful selection of electrophile and Lewis acid.[3] Lithiation of pyrrole **1** followed by reaction with various electrophiles has been reported to give 2-functionalized pyrroles in variable yields.[4,5] Efficient lithiations of *N*-vinylpyrrole[6] and *N*-BOC pyrrole[7] have also been reported. The magnesium amide bases (Hauser bases and bis-diamide-Mg species) offer a practical and economically attractive alternative to lithium bases, and various applications have been recently reviewed.[8]

We began our investigation by trying to extend the work of Kondo to *N*-phenylsulfonylpyrrole **1**, which was readily made by reacting pyrrole and phenylsulfonyl chloride in dichloromethane employing sodium hydroxide as a base, as described by Shastri.[9] A number of attempts to repeat the method of Ottoni[10] yielded no detectable sulfonylpyrrole **1**.

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[1] Kondo, Y.; Yoshida A.; Sakamoto T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2331−2332.

[2] Cadamuro, S.; Degani, I.; Dughera, S.; Fochi, R.; Gatti, A.; Piscopo, L. *J. Chem. Soc., Perkin Trans. 1* **1993**, 273−284.

[3] Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 3214−3219.

[4] Grieb, J. G.; Ketcha, D. M. *Synth. Commun.* **1995**, *25*, 2145−2154.

[5] Shiao, M.-J.; Shih, L.-H.; Chia, W.-L.; Chau, T.-Y. *Heterocycles* **1991**, *32*, 2111−2118.

[6] Malkina, A. G.; Tarasova, O. A.; Verkruijsse, H. D.; van der Kerk, A. C. H. T. M.; Brandsma, L.; Trofimov, B. A. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 18−21.

[7] Hasan, I.; Marinelli, E. R.; Li-Chang Chang Lin, Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157−164.

[8] Henderson, K. W.; Kerr W. J. *Chem. Eur. J.* **2001**, *7*, 3430−3437.

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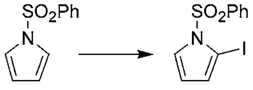
Our initial investigations employed an approximately 1 M solution of ^{i}PrMgBr, prepared in THF and subsequently stirred with $(^i\mathrm{Pr})_2$NH. Following exposure of pyrrole **1** to a 2-fold excess of this reagent and subsequent quenching with iodine, we isolated the desired 2-iodinated pyrrole **2** in 54% yield (Scheme 1).[11]

Scheme 1. Iodination of *N*-Phenylsulfonylpyrrole[a]



1 **2**

[a] Conditions are described in the text.

Though this represented a promising result, we found that stock solutions of the putative $(^i\mathrm{Pr})_2$NMgBr were significantly unstable at room temperature, turning dark brown and depositing a solid over the course of a few days. Given that during the magnesiation the amine is presumably regenerated, we wondered if the reaction could be made catalytic with respect to the amine. This proved to be the case; a 2.5-fold excess of ^{i}PrMgBr stirred with pyrrole **1** and to which 5 mol % (with respect to the pyrrole) of $(^i\mathrm{Pr})_2$NH was added yielded the iodosulfonylpyrrole **2** in a 65% isolated yield following an iodine quench. The 2-iodopyrrole **2** could be conveniently isolated and purified by recrystallization. Without any added $(^i\mathrm{Pr})_2$NH, no iodopyrrole was detected (although it has been previously been shown that ^{i}PrMgCl can deprotonate substituted pyridines at reflux in THF[12]). That the Mg-amide is the catalytically active species was supported by the replacement of $(^i\mathrm{Pr})_2$NH with triethylamine in the above procedure. No iodopyrrole was detected following workup, suggesting that the amine does not simply exert a deaggregation effect. Significantly, we found that catalytic diethylamine was also ineffective but can offer no explanation.

This approach would appear to be an obvious solution to the problem of equilibration of metal amide−carbon acid and metal carbanion−amine combinations, represented in Scheme 2, though we can find no description of such a previous approach. The closest is perhaps the recent results from the group of Eaton, wherein an effective excess of “butyl-magnesium” is employed to force the equilibrium represented in Scheme 2.[13] The approach described here represents a new and atom-economical methodology.

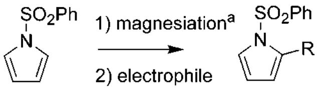
Scheme 2. Equilibration of Metal Amides/Carbon Acids

$$\mathrm{R_3C\text{-}Metal} + \mathrm{HNR'_2} \rightleftharpoons \mathrm{R_3CH} + \mathrm{Metal\text{-}NR'_2}$$

We found that the ^{i}PrMgBr, when prepared as a 1 M solution in THF, was only partially soluble at room temperature. The magnesiations described above had to be conducted at a minimum temperature of 45 °C to allow all the reactants to remain in solution, without which a good conversion does not occur. An improvement came with application of ^{i}PrMgCl. This Grignard reagent, when prepared as a 1 M solution in THF, is completely soluble at room temperature, allowing the subsequent metalation to be conducted at room temperature and giving an increase in the isolated yield of iodopyrrole **2** to 75%. Wondering if a potentially non-redox-active Grignard reagent would further improve the yields, we repeated the magnesiation employing an approximately 1 M solution of PhMgCl, but yields were reduced.

We examined the reaction of the magnesiopyrrole with a number of different electrophiles as shown in Table 1. With TMS−Cl, no reaction was detected, but with the more reactive TMS−OTf, a 57% isolated yield of the TMS substituted pyrrole **3** was obtained. Allylation, ring opening of γ-butyrolactone, formylation,[14] and addition to carbonyl groups all proceeded to give the expected products **4**−**8** in moderate isolated yields. Addition of trimethyl or triisopropyl borate to the magnesiopyrrole gave an immediate exothermic

Table 1. Results of Addition of Magnesio-pyrrole to Different Electrophiles



electrophile	R	product	yield[b](%)
TMS−OTf[c]	−TMS	**3**	57
γ-butyrolactone[d]	$-\mathrm{CO(CH_2)_3OH}$	**4**	52 (78)
allyl bromide[e]	$-\mathrm{CH_2CH{=}CH_2}$	**5**	52 (78)
DMF[f]	−CHO	**6**	48 (73)
acetone[g]	$-\mathrm{C(CH_3)_2OH}$	**7**	45 (97)
benzaldehyde[h]	−CHOHPh	**8**	57 (75)
trimethyl borate[i]	$-\mathrm{B(OH)_2}$[j]	**9**	5
iodobenzene[k]	$-\mathrm{C_6H_5}$	**10**	73
2-chloropyridine[l]	−pyrid-2-yl	**11**	24 (53)
2-chloroquinoline	−quinolin-2-yl[m]	**12**	32 (44)

[a] Magnesiation protocol: either **A** (2.5 equiv of ^{i}PrMgBr (1 M in THF)/5 mol % $^i\mathrm{Pr_2NH}$/16 h/50 °C) or **B** (2.5 equiv of ^{i}PrMgCl (1 M in THF)/5 mol % $^i\mathrm{Pr_2NH}$/16 h/rt). [b] Isolated yield. Yield based on recovered starting material shown in brackets. [c] **A**, then 1.2 equiv of TMSOTf, 0 °C, 20 min. [d] **A,** then 1.5 equiv of γ-butyrolactone/1 h/50 °C. [e] **A,** then allyl bromide/1 h/50 °C. [f] **A**, then DMF/1 h/50 °C. [g] **A**, then acetone/0.5 h/50 °C. [h] **A**, then PhCHO/0.5 h/50 °C. [i] **A**, then $\mathrm{B(OMe)_3}$/1 h/50 °C. [j] *N*-Desulfonylated boronic acid isolated. [k] **B**, then 2 equiv of iodobenzene/5 mol % $\mathrm{Pd(Ph_3P)_4}$/45 h/rt. [l] **B**, then 0.5 equiv of $\mathrm{ZnCl_2}$/2 equiv of 2-chloropyridine/2 mol % $\mathrm{PdCl_2dppf}$/48 h/rt. [m] **B**, as in footnote l, but employing 2-chloroquinoline.

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(9) Zelekin, A.; Shastri, V. R.; Langer, R. *J. Org. Chem.* **1999**, *64*, 3379−3380.

(10) Ottoni, O.; Cruz, R.; Alves, R. *Tetrahedron* **1998**, *54*, 13915−13928.

(11) This compound is described in the literature, though no characterization is given. See: Sakamoto, T.; Ohsawa, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2323−2326.

(12) Bonet, V.; Mongin, F.; Trécourt, F.; Quéguiner, G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4245−4249.

(13) Zhang, M.-X.; Eaton P. E. *Angew. Chem., Int. Ed.* **2002**, *41*, 2169−2171.

(14) Characterization data for product **6** were identical to those published; see: Muratake, H., Natsume, M. *Heterocycles* **1990**, *31*, 683−690.

reaction. Following hydrolysis and workup, however, we isolated principally the parent unsubstituted pyrrole **1**. Small amounts of what appeared to be the desulfonylated pyrrole-2-boronic acid **9** were isolated, but we have not been able to improve the yield of this product above ca. 5%.

We investigated extension of the methodology to provide aryl- and heteroaryl-substituted pyrroles. The magnesiopyrrole prepared from pyrrole **1** and either ^{i}PrMgCl or ^{i}PrMgBr was found to undergo a Kumada-type coupling with iodobenzene in the presence of catalytic Pd($Ph_3P)_4$ to give the 2-phenylsulfonylpyrrole **10**.[15]

Heteroaryl-substituted pyrroles offer attractive targets, as they can provide novel physical properties, particularly when they have the potential for metal complexation.[16] Attempts to cross-couple 2-chloropyridine with the magnesiopyrrole, prepared as described above, failed using either Pd($Ph_3P)_4$ or $NiCl_2$dppe catalysis. 2-Bromopyridine and even 2-iodopyridine[17] failed to give any detectable cross-coupling product with the magnesiopyrrole employing palladium catalysis.

A solution to this impasse was found by employing a variation on conditions recently described[18] to allow the heteroaryl-coupling of furyllithium species. Thus, pretreatment of the magnesiopyrrole with a submolar equivalent of zinc chloride followed by 2-chloropyridine and finally catalytic $PdCl_2$dppf gave an immediate exothermic reaction. Following workup, the desired 2-(pyrid-2-yl)pyrrole **11** was isolated in 24% yield (54% on the basis of recovered starting material) and proved to have identical properties to those described in the literature.[19]

This methodology was extended to provide the novel 2-quinolyl-substituted phenylsulfonylpyrrole **12**, the structure of which was confirmed by single-crystal X-ray analysis carried out on the perchlorate salt (Figure 1). The structure shows a pyramidal arrangement of substituents around the nitrogen, consistent with previous crystal structures describing compounds containing the *N*-phenylsulfonyl substructure.[20]

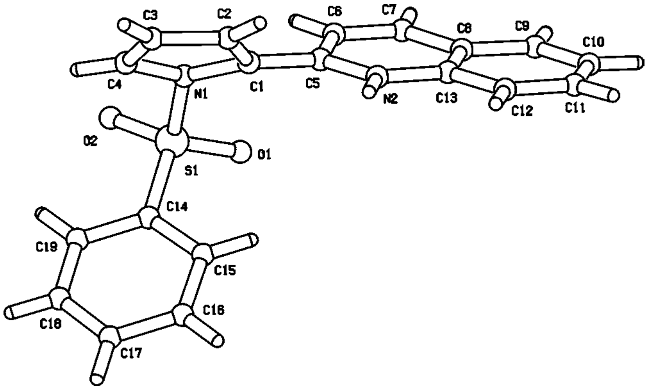
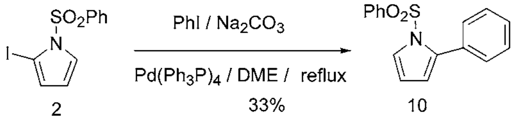


Figure 1. PLUTO diagram for **12**. For clarity, the perchlorate anion and H-bonded EtOH have been omitted.

Attempts to undertake a palladium-catalyzed Kumada-type coupling between the magnesiopyrrole and 3-bromopyridine failed to give any detectable cross coupling. Even addition of a submolar equivalent of zinc chloride prior to addition of the 3-bromopyridine and $PdCl_2$dppf gave, following workup, only trace quantities of the desired pyrid-3-yl coupled product as judged by GCMS analysis.

Since we were able to readily prepare gram quantities of 2-iodopyrrole **2** without any chromatography using our methodology, we investigated application of this compound in coupling reactions. Attempted Stille-type coupling with tributylstannylbenzene gave no detectable product. Application of stoichiometric copper(I) thiophenecarboxylate[21] (CuTC) (which we have previously found useful for accomplishing otherwise refractory heteroaryl Stille-type couplings[22]) to a mixture of iodopyrrole **2** and tributylstannylbenzene in *N*-methylpyrrolidine gave no detectable reaction. In addition, attempts to achieve the low-temperature homocoupling of the 2-iodopyrrole **2** using the general method of Liebeskind[23] also failed, the only isolated product being the deiodinated pyrrole **1**. Suzuki-type coupling of the iodopyrrole with phenylboronic acid was found to be successful, yielding the 2-phenylpyrrole **10**, identical to that prepared from the Kumada reaction described above, in a yield of 33% (Scheme 3).

Scheme 3. Suzuki Coupling of 2-Iodopyrrole



In conclusion, a novel and highly atom-efficient protocol for the functionalization of *N*-sulfonylpyrrole has been developed by utilizing a Grignard reagent as a thermodynamic base and catalytic amine to function as the kinetically

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[15] This compound is described in ref 4, though the spectroscopic details differ from those of the compound we have isolated.

[16] See for example: Wu, F.; Chamchoumis, C. M.; Thummel, R. P. *Inorg. Chem.* **2000**, *39*, 584−590.

[17] We found that this was best prepared from 2-bromopyridine by the exchange method of Quéguiner (Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron* **2000**, *56*, 1349−1360) using ^{i}PrMgCl and subsequent quenching with iodine. Intriguingly, the apparently equivalent ^{i}PrMgBr gave no insertion of magnesium and only bromopyridine was isolated.

[18] Gauthier, D. R., Jr.; Szumigala, R. H., Jr.; Dormer, P. G.; Armstrong, J. D., III; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *3*, 375−378.

[19] This compound was previously made by a copper-mediated addition of the lithio-pyrrole derived from **1** to an acyl-pyridinium species followed by oxidation, as described in ref 5.

[20] The geometry of a number of structures containing *N*-phenylsulfonyl-pyrrole and -indole components has been reviewed (Beddoes, R. L.; Dalton, L.; Joule, J. A.; Mills, S. O.; Street, J. D.; Watt, C. I. F. *J. Chem. Soc., Perkin Trans. 2* **1986**, 787−797).

[21] Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748−2749.

[22] Dinsmore, A.; Garner, C. D.; Joule, J. A. *Tetrahedron* **1998**, *54*, 3291−3302.

[23] Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312−2313.

competent mediator. This combination has been applied to provide various 2-substituted phenylsulfonylpyrroles. Aryl and heteroaryl couplings of the putative intermediate magnesiopyrrole are possible, though conditions to achieve this need to be carefully selected to have any success.

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Supporting Information Available: Experimental procedures, product characterization, and a CIF file containing details of the XRD characterization of compound **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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