PERKIN 1
COMMUNICATION

Magnesiation of indoles with magnesium amide bases

Yoshinori Kondo,* Akihiro Yoshida and Takao Sakamoto*

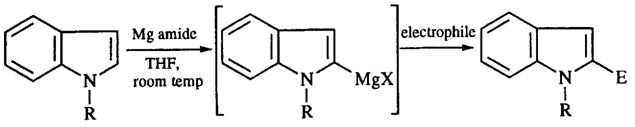
Faculty of Pharmaceutical Sciences, Tohoku University, Aobayama, Aoba-ku, Sendai 980-77, Japan

1-Substituted indole derivatives are deprotonated with Hauser bases (R_2NMgBr) or magnesium diamide [$(R_2N)_2Mg$] to give magnesioindoles which are then reacted with electrophiles.

Metallation at the 2-position of indoles, *e.g.* using lithiation as a synthetic route to 2-substituted indoles,[1] has been studied since electrophilic substitution reactions ordinarily occur at the 3-position of the indole ring. Many removable substituents at the 1-position have been investigated and the choice of substituent depends on requirements for compatibility with other functional groups for synthetic purposes. Usually lithiation is conducted at low temperature due to the instability of the lithiating reagent or intermediary lithio species.

Recently, Eaton *et al.* reported a facile method for magnesiation of benzene derivatives with alkoxycarbonyl or carbamoyl groups using magnesium amides.[2] The method was applied to magnesiation of pyridines, which were functionalized under mild conditions.[3] In connection with our recent studies on the metallation of indole derivatives,[4] we became interested in the magnesiation of indoles with magnesium amides and studied the scope and limitations of this proton–magnesium exchange reaction.

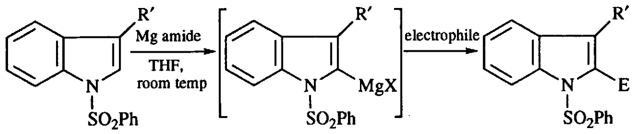
First, magnesiation of 1-phenylsulfonylindole **1a** with two kinds of bases, $(Pr^i_2N)_2Mg$ and Pr^i_2NMgBr, at room temperature followed by reaction of the produced 2-magnesioindole **2a** with benzaldehyde or iodine gave the corresponding substituted indoles **3a,b** in excellent yields (Table 1, Scheme 1). Similar magnesiation of 1-*tert*-butoxycarbonylindole **1b** and the subsequent reaction of **2b** with iodine gave 1-*tert*-butoxycarbonyl-2-iodoindole **3d** in 52% yield. However, the reaction of the same magnesioindole **2b** with benzaldehyde failed to give the desired alcohol **3c**. The magnesiation of 1-methylindole **1c** did not proceed even at elevated temperature.



1a–c **2a, b** **3a–d**

Scheme 1

The phenylsulfonyl group appeared to be a promising protecting and activating group for this magnesiation reaction, so we examined further reactions using 1-phenylsulfonylindoles as substrates (Table 2, Scheme 2).



1a, 4a–c **5a–h**

Scheme 2

1-Phenylsulfonylindole **1a** was converted to the magnesioindole **2a** and reactions with other electrophiles were examined. The reaction with carbon dioxide followed by treatment with diazomethane gave the ester **5a** in 58% yield. Alkylation with allyl bromide gave the 2-allyl derivative **5b** in 44% yield and the palladium catalysed cross coupling reaction with iodobenzene proceeded to give the 2-phenyl derivative **5c** in 62% yield. Substitution at the 3-position of indoles did not affect the magnesiation, and 3-methyl-1-phenylsulfonylindole **4a** reacted with $(Pr^i_2N)_2Mg$ and the subsequent reaction with benzaldehyde gave the corresponding 2,3-disubstituted indole **5d** in 80% yield. Finally, compatibility with electrophilic functional groups was examined. Methyl 1-phenylsulfonylindole-3-carboxylate **4b** was treated with $(Pr^i_2N)_2Mg$ followed by iodine to give the 2-iodo derivative **5e** in 45% yield and treatment of the magnesioindole with carbon dioxide–diazomethane gave the dimethyl indole-2,3-dicarboxylate **5f** in 12% yield. The indole-3-carbonitrile **4c** was treated with Pr^i_2NMgBr and subsequent reaction with iodine gave the 3-cyano-2-iodo derivative **5g** in 22% yield.

Magnesiation of these functionalized indoles requires further optimization of the reaction conditions, however the present method seems to have potentially wide applications for the functionalization of indoles at the 2-position. Further investigations are in progress.

Experimental

2-Iodo-1-phenylsulfonylindole 3b

Under an argon atmosphere, diisopropylamine (0.202 g, 2 mmol) was added to a mixture of 1.0 M dibutylmagnesium in heptane (1.0 ml, 1 mmol) and dry THF (5 ml) and the mixture was stirred at room temperature for 4 h. 1-Phenylsulfonylindole

Table 1 Magnesiation of 1-substituted indoles

Starting material				Product		
1	R	Mg amide	Electrophile	3	E	Yield (%)
a	SO_2Ph	$(Pr^i_2N)_2Mg$	PhCHO	a	CH(OH)Ph	93
a	SO_2Ph	$(Pr^i_2N)_2Mg$	I_2	b	I	85
a	SO_2Ph	Pr^i_2NMgBr	PhCHO	a	CH(OH)Ph	83
a	SO_2Ph	Pr^i_2NMgBr	I_2	b	I	60
b	CO_2Bu^t	$(Pr^i_2N)_2Mg$	PhCHO	c	CH(OH)Ph	0
b	CO_2Bu^t	$(Pr^i_2N)_2Mg$	I_2	d	I	52
c	Me	$(Pr^i_2N)_2Mg$	I_2	—	I	0

Table 2 Magnesiation of 3-substituted 1-phenylsulfonylindoles

Starting material				Product		
1,4	R′	Mg amide	Electrophile	**5**	E	Yield (%)
1a	H	$(\mathrm{Pr^i}_2\mathrm{N})_2\mathrm{Mg}$	$\mathrm{CO_2}$–$\mathrm{CH_2N_2}$	**a**	$\mathrm{CO_2Me}$	58
1a	H	$(\mathrm{Pr^i}_2\mathrm{N})_2\mathrm{Mg}$	$\mathrm{CH_2{=}CHCH_2Br}$	**b**	$\mathrm{CH_2CH{=}CH_2}$	44
1a	H	$(\mathrm{Pr^i}_2\mathrm{N})_2\mathrm{Mg}$	PhI–$\mathrm{Pd(PPh_3)_4}$	**c**	Ph	62
4a	Me	$(\mathrm{Pr^i}_2\mathrm{N})_2\mathrm{Mg}$	PhCHO	**d**	CH(OH)Ph	80
4b	$\mathrm{CO_2Me}$	$(\mathrm{Pr^i}_2\mathrm{N})_2\mathrm{Mg}$	$\mathrm{I_2}$	**e**	I	45
4b	$\mathrm{CO_2Me}$	$(\mathrm{Pr^i}_2\mathrm{N})_2\mathrm{Mg}$	$\mathrm{CO_2}$–$\mathrm{CH_2N_2}$	**f**	$\mathrm{CO_2Me}$	12
4c	CN	$\mathrm{Pr^i}_2\mathrm{NMgBr}$	$\mathrm{I_2}$	**g**	I	22

1a (0.129 g, 0.5 mmol) in dry THF (2 ml) was added to the mixture and stirring was continued at room temperature for 1.5 h. Iodine (0.38 g, 1.5 mmol) in dry THF (2 ml) was added and the mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the residue was diluted with aqueous $\mathrm{NH_4Cl}$. The mixture was extracted with $\mathrm{CH_2Cl_2}$ (3 × 30 ml). The organic layer was dried over $\mathrm{MgSO_4}$ and the $\mathrm{CH_2Cl_2}$ was removed. The crude material was purified by $\mathrm{SiO_2}$ column chromatography using hexane–$\mathrm{Et_2O}$ (4:1) as the eluent, to give a colourless solid (163 mg, 85%); δ_H(300 MHz; $\mathrm{CDCl_3}$) 6.98 (1 H, s), 7.20–7.24 (2 H, m), 7.26–7.43 (3 H, m), 7.51 (1 H, t, *J* 7.3†), 7.89 (2 H, d, *J* 8.1), 8.27 (1 H, d, *J* 8.4).

References

1 G. W. Rewcastle and A. R. Katritzky, *Adv. Heterocycl. Chem.*, 1993, **56**, 155.

2 P. E. Eaton, C.-H. Lee and Y. Xiong, *J. Am. Chem. Soc.*, 1989, **111**, 8016.

3 (*a*) W. Schlecker, A. Huth, E. Ottow and J. Mulzer, *Liebigs Ann. Chem.*, 1995, 1441; (*b*) W. Schlecker, A. Huth, E. Ottow and J. Mulzer, *J. Org. Chem.*, 1995, **60**, 8414.

4 (*a*) Y. Kondo, A. Yoshida, S. Sato and T. Sakamoto, *Heterocycles*, 1996, **42**, 105; (*b*) T. Sakamoto, Y. Kondo, N. Takazawa and H. Yamanaka, *Heterocycles*, 1993, **36**, 941; (*c*) T. Sakamoto, Y. Kondo, N. Takazawa and H. Yamanaka, *Tetrahedron Lett.*, 1993, **34**, 5955; (*d*) Y. Kondo, N. Takazawa, A. Yoshida and T. Sakamoto, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1207.

Paper 6/04599E
Received 2nd *July* 1996
Accepted 29*th July* 1996

---

† *J* Values in Hz.