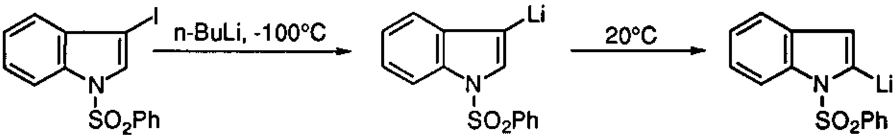
HALOGEN-MAGNESIUM EXCHANGE REACTION OF IODOINDOLE DERIVATIVES

Yoshinori Kondo, Akihiro Yoshida, Shuichiroh Sato, and
Takao Sakamoto*

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

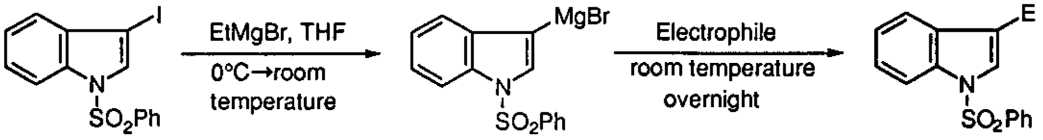
Abstract - Halogen-magnesium exchange reaction of iodoindoles with ethylmagnesium bromide in THF undergoes smoothly to give indolylmagnesium bromides which react with various electrophiles.

Halogen-lithium exchange reaction has been extensively studied for the preparation of aromatic and heteroaromatic lithium compounds.[1] Lithioindoles have been prepared using halogen-lithium exchange reaction of haloindoles, however preparation of 3-lithio-*N*-phenylsulfonylindole from the 3-iodoindole derivative can be done under strictly controlled reaction conditions (-100° C),[2] and at higher temperature, the 3-lithioindole are known to isomerize to the corresponding 2-lithioindole. The isomerization is avoidable only when a bulky group such as *tert*-butyldimethylsilyl group was introduced as a protecting group of indole.[3]



Oxidative addition reaction of metallic magnesium to haloaromatics and haloheteroaromatics has been widely used for a preparative method of the corresponding magnesium drivatives.[4] On the other hand, halogen-magnesium exchange reaction of haloaromatic compounds with alkylmagnesium halides is also known,[5] however its synthetic utility has not yet optimized. Comparing with lithioindoles, preparation and reaction of magnesioindoles received little attention and halogen-magnesium exchange reaction of 3-haloindoles has not yet appeared to the best of our knowledge. In connection with our recent studies on indole metal chemistry,[6] we investigated halogen-magnesium exchange reaction of iodoindoles with easily removable *N*-phenylsulfonyl group.

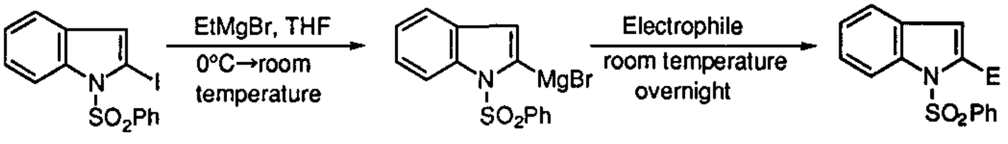
3-Iodo-1-phenylsulfonylindole (**1**) was treated with ethylmagnesium bromide in THF at 0° C, then the mixture was allowed to warm to room temperature and was stirred for 30 min. Benzaldehyde was allowed to react with the magnesioindole (**2**) to give the corresponding alcohol (**3a**) in 82%. Propionaldehyde also reacted smoothly to give the alcohol (**3b**) in 65%. Reaction with paraformaldehyde and reaction with carbon dioxide followed by treatment with diazomethane gave indole-3-methanol derivative (**3c**) in 48% and indole-3-carboxylate (**3d**) in 85% respectively. Cross-coupling reaction of **2** with iodobenzene in the presence of $Pd(PPh_3)_4$ was succcessful and 3-phenylindole (**3e**) was obtained in 50%. The 3-magnesioindole generated by the halogen-magnesium exchange reaction seems thermally stable to some extent and no isomerization to the 2-position was observed.



1 **2** **3a-e**

3	Electrophile	E	Yield (%)
a	PhCHO	CH(OH)Ph	82
b	EtCHO	CH(OH)Et	65
c	$(CH_2O)n$	CH_2OH	48
d	CO_2/CH_2N_2	COOMe	85
e	PhI, $Pd(PPh_3)_4$	Ph	50

Magnesiation at 2-position of indole was also successful and the magnesioindole reacted with various electrophile to give functionalized indoles (**6a**-**e**) in fair to good yields.

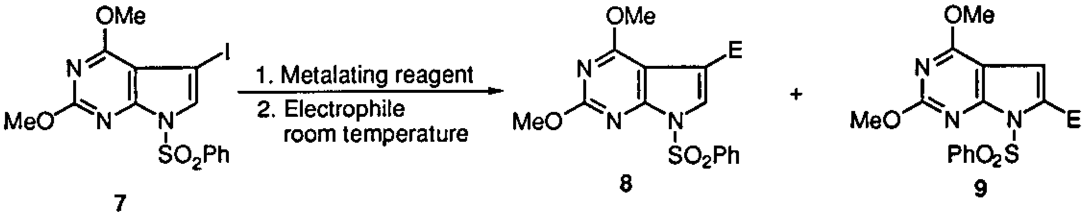


4 **5** **6a-e**

6	Electrophile	E	Yield (%)
a	PhCHO	CH(OH)Ph	85
b	EtCHO	CH(OH)Et	63
c	$(CH_2O)_n$	CH_2OH	43
d	CO_2	COOH	51
e	PhI, $Pd(PPh_3)_4$	Ph	52

Next, we investigated magnesiation at β-position of pyrrolo[2,3-*d*]pyrimidine in conjunction with our studies on biologically active pyrrolopyrimidines,[7] especially interest on synthesis of cadeguomycin.[8] Priror to this work, we observed that the lithiation at β-position of iodopyrrolopyrimidine *via* halogen-lithium exchange reaction accompanies isomerization to α-position. For example, trapping the lithio species with benzaldehyde gave a mixture of two isomeric alcohol derivatives (**8a**,**9a**).

On the other hand, halogen-magnesium exchange reaction of **7** proceeded smoothly to give β-magnesio derivative, and trapping with benzaldehyde gave the alcohol (**8a**) in 76% yield with no isomerization product (**9a**). The magnesio derivative was allowed to react with carbon dioxide and then with diazomethane to give pyrrolopyrimidine-5-carboxylate (**8b**).



Metalating reagent	Conditions	Electrophile	E	8	Yield(%)	9	Yield(%)
n-BuLi	-78°C, 1 h	PhCHO	CH(OH)Ph	a	50	a	8
EtMgBr	0°C, 0.5 h	PhCHO	CH(OH)Ph	a	76	a	0
EtMgBr	0°C, 0.5 h	CO_2/CH_2N_2	COOMe	b	44	b	0

As described above, halogen-magnesium exchange reaction of iodoindoles with ethylmagnesium bromide was proved to be a convenient and facile metallating method, which allow us to introduce carbon functionalities onto indoles and its aza analogues.

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examined oxidative addition of metallic magnesium (turnings) to the 3-iodoindole, however the reaction was sluggish and unsuccessful.

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9. Typical procedure : **α-Phenyl-1-phenylsulfonylindole-3-methanol** - All operations were performed under argon atmosphere. To a mixture of 3-iodo-1-phenylsulfonylindole (0.38 g, 1.0 mmol) and dry THF (5 ml), 1M EtMgBr solution in THF (1.2 mmol) was added at 0℃ and the mixture was stirred for 30 min. The mixture was then allowed to warm to room temperature and was stirred for 30 min. Benzaldehyde (0.12 ml, 1.2 mmol) was added to the mixture and stirring was continued overnight. After reaction, the solvent was removed and the residue was diluted with H_2O. The mixture was extracted with CH_2Cl_2 and the CH_2Cl_2 layer was dried over $MgSO_4$. The CH_2Cl_2 was evaporated and the residue was purified by SiO_2 column chromatography using hexane-Et_2O (4:1) as an eluent. Pale yellow viscous oil (0.30 g, 82%) was obtained; 300 MHz ^{1}H-nmr (300 MHz, $CDCl_3$) δ: 2.20-2.22 (1H, d, *J*=4.4 Hz), 6.02-6.03 (1H, d, *J*=3.3 Hz), 7.15-7.18 (1H, m), 7.26-7.56 (11H, m), 7.86-7.89 (2H, m), 7.96-7.99 (1H, d, *J*=8.42).

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