THE DIRECTED LITHIATION OF ISOGRAMINE AND SUBSEQUENT REACTIONS WITH ELECTROPHILES IN THE PREPARATION OF 2-SUBSTITUTED ISOGRAMINE DERIVATIVES

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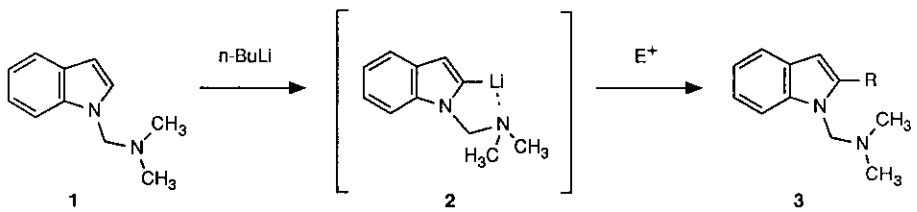
Abstract - Isogramine (**1**) undergoes 2-lithiation on reaction with *n*-butyllithium under very practical and straightforward reaction conditions. This 2-lithio species (**2**) reacts with aromatic carbonyl compounds to afford in good yields 2-substituted isogramines(**3**).

There has been a long standing need for directing groups that permit the lithiation of indole at the 2-position for subsequent functionalization and that could be removed under mild conditions. The 1-benzenesulfonyl[1a] and the 1-lithiocarboxylate[1b] functional groups are two of the best removable directing groups for indole. These groups suffer from the inconvenience of requiring low reaction temperatures (-78 °C) and with the 1-lithiocarboxylate group, the extremely pyrophoric *t*-butyllithium must be used. Additionally, the benzenesulfonyl group is susceptible to nucleophilic cleavage. This report describes a new lithiation directing group which permits the lithiation of indole under straightforward reaction conditions, and that does not suffer from the difficulties described above. This directing group, however, could be removed in only two examples where a 2-carbonyl group facilitated the deprotection. The reported use of 1-(dimethylamino)methyl as a directing group for the lithiation of imidazole, benzimidazole, pyrazole, and carbazole by Katritzky and co-workers[2] has prompted us to report our results in the use of the 1-(dimethylamino)methyl group as a lithiation directing group for indole.

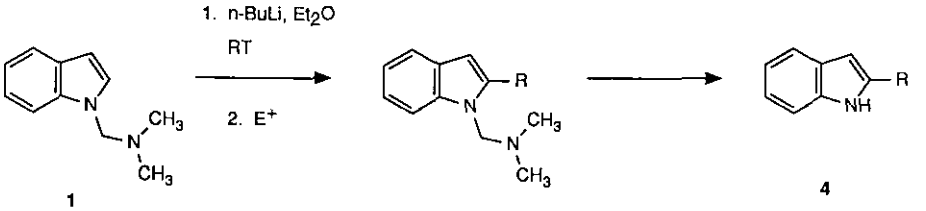


1 **2** **3**

We chose to examine the utility of the 1-(dimethylamino)methyl group as a 2-lithiation director for indole. The 1-(dimethylamino)methyl group, unlike 1-benzenesulfonyl, is stable to the nucleophilic addition of bases and is an efficient director for ortho-lithiation of aromatic systems. In addition, the 1-(dimethylamino)methyl group could be

readily introduced by subjecting indole to Mannich reaction conditions to afford isogramine (**1**).[3]

The lithiation of isogramine (**1**) takes place readily with *n*-butyllithium (0 °C, THF, 1.5 h) as evidenced by deuterium incorporation on D_2O quench. In a more practical procedure, isogramine (115 mmole scale, 0.25 M in ether) was treated with *n*-butyllithium at room temperature (RT) under nitrogen for 2 h, followed by the addition of benzophenone, and after 2 h the indole **3a** was isolated in 71% yield. The 2-substituted indoles **3b**, **3c**, and **3d** were similarly prepared by the reaction of **2** at RT or 0 °C with benzaldehyde, 4-pyridinecarboxaldehyde, and *N*,4-dimethoxy-*N*-methylbenzamide (**5**),[4,5] respectively. Attempted deprotection of **3a** under a variety of acidic, basic, or reductive conditions gave recovered starting material or mixtures. However, the indole **3d** was deprotected to afford **4d** with sodium methoxide in methanol at RT for 2 h in 79% yield or with 3N HCl at reflux for 2 h in 71% yield. More expeditiously, the 2-substituted indoles **4d** and **4e** were prepared in a one pot reaction by treatment of the anion **2** with benzamide **5** or carbon dioxide at 0 °C, addition of methanol, and stirring at RT for 3-18 h. Workup and recrystallization afforded **4d** and **4e** in 63% and 50% yield, respectively. We posit that the 2-carbonyl group of **4d** and **4e** stabilizes the indole ring to electrophilic reactions, prevents further reaction, and permits the isolation of the deprotected indoles in good yield. The isogramine **3a** does not possess a stabilizing group and, therefore, undergoes further side reactions on attempted deprotection to the indole **4a**.



1 **4**

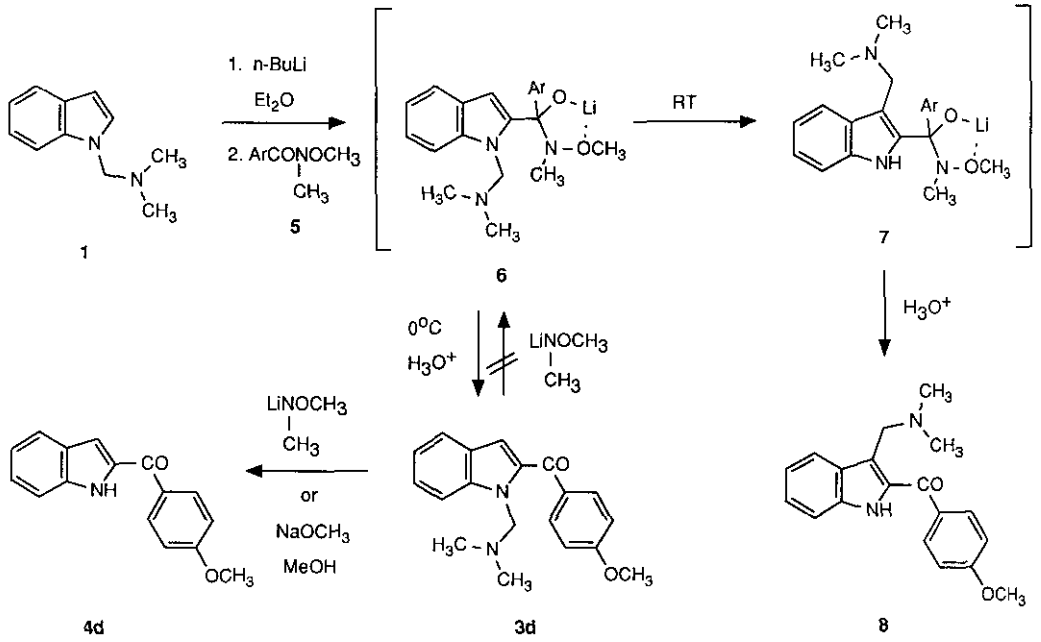
3a R = -C(OH)Ph_2 71%
3b -CH(OH)Ph 64%
3c -CH(OH)-(4-pyridyl) 56%
3d -COC_6H_4-4-OCH_3 58%

4d R= -COC_6H_4-4-OCH_3 63%[6]
4e -COOH 50%[6]

An isogramine-gramine rearrangement was noted in two examples. When the anion **2** was treated with benzamide **5** at 0 °C, stirred overnight at RT, quenched with saturated ammonium chloride, and worked up, the gramine derivative **8** was obtained in 64% yield, instead of isogramine **3d**. However, the isogramine **3d** was the sole product obtained when the benzamide **5** was reacted with the anion **2** for 1 h at 0 °C and worked up. It seems unlikely that the gramine **8** results through the rearrangement of isogramine **3d**, since reaction of this deactivated 2-benzoylindole with the Mannich base should be slow.

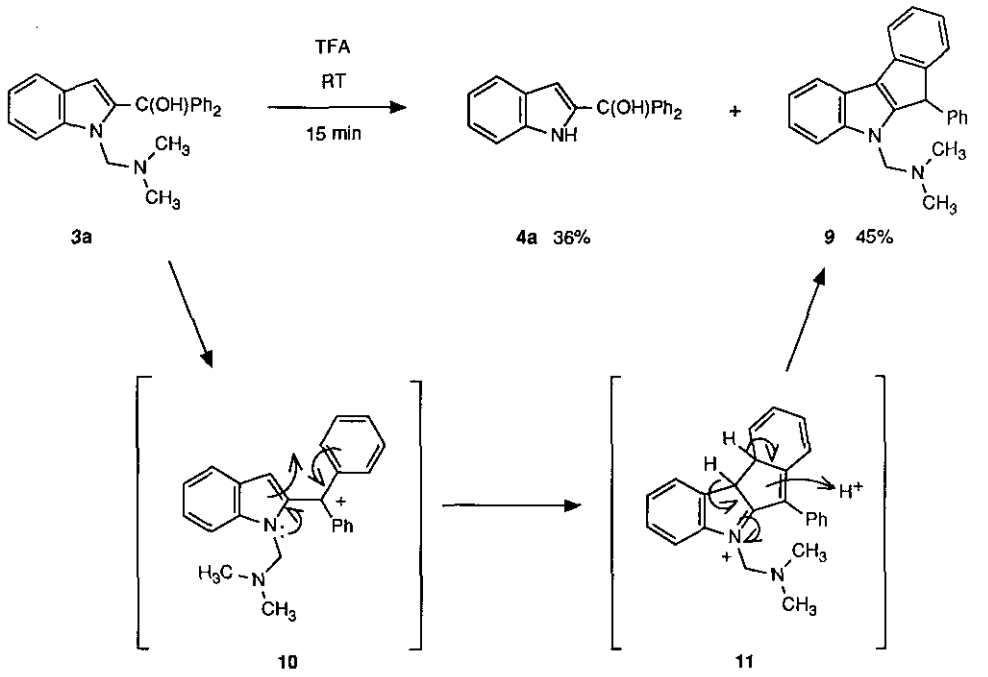
A more likely explanation for the formation of the gramine **8** involves rearrangement of the stabilized complex **6**[4]

to **7** when the reaction is warmed to room temperature. Evidence which supports the rearrangement of the complex **6** to **7** rests on our inability to transform the isogramine **3d** into the gramine **8**. When **3d** was placed into reaction conditions under which **8** was formed ($LiN(CH_3)OCH_3$, Et_2O, RT, 18 h), the sole product obtained was the deprotected **4d** in 48% yield, along with recovered **3d**. Additionally, treatment of the anion **2** with benzophenone at RT and then at reflux for 8 h gave on isolation the isogramine **3a** (17%) and the analogous gramine derivative (66%).



The deprotection of the indole **3a** with TFA was further studied, since the reaction of **3a** in TFA at room temperature immediately gave a dark red solution. Workup of the reaction after 15 minutes gave a mixture of the deprotected indole **4a** and the tetracycle **9**. The carbonium mediated reactions of the indolecarbinol **4a** have been studied by Dolby and Lord.[7] Numerous products where isolated, however, none of the tetracycle analogous to **9** was detected. The cyclization of **3a** to **9** is reminiscent of the classic acid catalyzed thermal cyclization of triphenylcarbinol presumably via trityl cation to 9-phenylfluorene.[8] A proposed mechanism for the formation of **9** is outlined below. The cyclization of the initially formed carbonium **10** is envisioned to occur by assist of the indole nitrogen lone pair of electrons as shown in the scheme below. Rearomatization of both the indolo and the benzo ring of **11** must be the driving force for the formation of the tetracycle **9**.

Our results show that for indole the 1-(dimethylamino)methyl group is an efficient 2-lithiation director and that these reactions provide in good yields under practical conditions the desired 2-substituted isogramines. The directing group in the isogramines **3** could be removed in two examples (**4d** and **4e**) under basic conditions where a stabilizing 2-carbonyl group was present. In the absence of the stabilizing group, for example in **3a**, the directing



group could not be removed cleanly under a variety of conditions. This lithiation reaction should prove useful in the synthesis of 2-substituted gramine derivatives, such as **8**, via the isogramine-gramine rearrangement reaction.

REFERENCES AND FOOTNOTES

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2. A. R. Katritzky, G. W. Rewcastle, and W.-Q. Fan, J. Org. Chem., 1988, 53, 5685. A. R. Katritzky, G. W. Rewcastle, and L. M. Vazquez de Miguel, J. Org. Chem.,1988, 53, 794.
3. S. Swaminathan and K. Narasimhan, Chem. Ber., 1966, 99, 889.
4. S. Nahm and S. M. Weinreb, Tetrahedron Lett., 1981, 22, 3815.
5. Addition of **2** to *p*-anisoyl chloride in ether at -78 °C, following Sundberg's conditions[1a], gave a mixture (tlc, nmr).
6. Overall yield from **1** in a one pot reaction.
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