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REACTIONS OF 1-METHOXY-3-(2-NITROVINYL)INDOLE WITH NUCLEOPHILES: AN INTERESTING SOLVENT EFFECT AND A NOVEL PREPARATION OF 3-SUBSTITUTED 1-METHOXYINDOLES[1]

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Abstract — Nucleophiles react with 1-methoxy-3-(2-nitrovinyl)indole (**3**) at the 2-position regioselectively in a dipolar aprotic solvent (DMF or HMPA), while in THF they undergo Michael addition to the β-carbon of nitrovinyl side chain. Depending on bases employed, the resultant Michael addition products (**6d**, **10**, and **11**) are found to undergo interesting cyclizations to give novel 3-substituted 1-methoxyindoles (**7**, **9**, and **12**).

We found that 1-methoxyindoles (**1a**–**f**, Scheme 1) having an electron withdrawing group at the 3-position undergo nucleophilic substitution reaction[2] with various nucleophiles in DMF, culminating in a novel method for preparing 2-substituted indoles (**2a**–**f**), which are hardly available by the conventional electrophilic substitution reaction[3] of indoles. In order to determine the scope of the method, we then selected 1-methoxy-3-(2-nitrovinyl)indole (**3**) as a substrate.

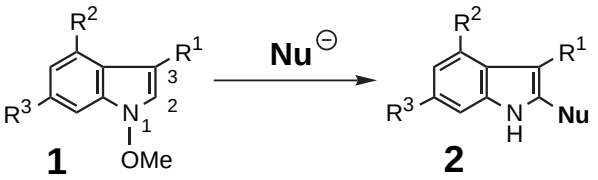
The compound (**3**), readily available from commercially available 2,3-dihydroindole in three steps in 49% overall yield,[4a,b] reacted with NaOMe and NaOPr in DMF at 80—92°C to provide 2-methoxy- (**4a**) and 2-propoxy-3-(2-nitrovinyl)indole[4a] (**4b**) in 85 and 55% yields, respectively, as expected. In sharp contrast, employing THF as a solvent instead of DMF, the same reactions at 0°C produced 1-methoxy-3-(1-methoxy-2-nitroethyl)indole (**6a**, Michael addition product) and **6b** in 90 and 92% yields, respectively. In these reactions, minor products were formed, but the absences of **4a** and **4b** among them were confirmed by taking ^{1}H-NMR spectrum for every fraction of products.

Solvents are known to play an important role in governing the reaction paths and products in some cases.[5] Our above example suggested that dipolar aprotic solvent (DMF or HMPA) directs nucleophilic attack to the 2-position of **3** with concomitant liberation of the 1-methoxy group, while THF leads them to Michael addition at the β-carbon of nitrovinyl side chain.

In order to confirm the assumption, we further compared the reaction of **3** with a few additional nucleophiles. As a result, the reaction with sodium allyl oxide in DMF at 86°C provided **4c** and **5a** in 65 and 6% yields, respectively. However, the same reaction in THF at 0°C produced **6c** in 58% yield without formation of 2-substituted indoles (**4c** and **5a**).

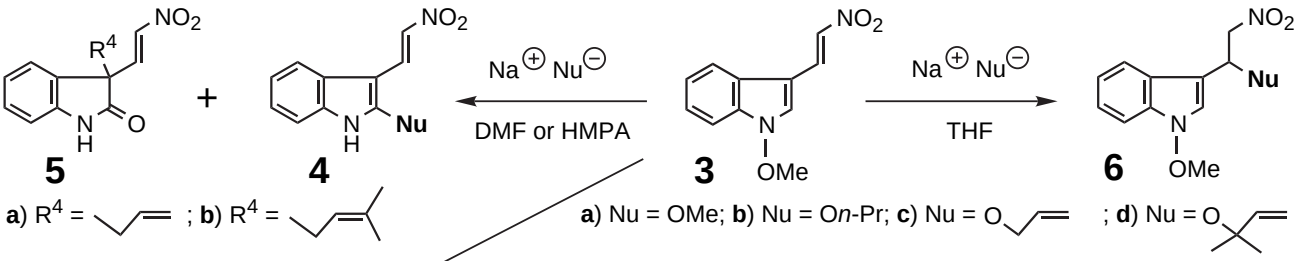
Similarly, in the reaction with potassium 1,1-dimethylallyl oxide, **3** provided rearranged product (**5b**) *via* **4d** in 39% yield by the reaction at 88°C in HMPA. On the other hand, in THF at 0°C, **3** afforded **6d** in 81% yield. Interestingly, when the latter reaction was carried out in THF at reflux, a 55% yield of novel

Scheme 1



1 **2**

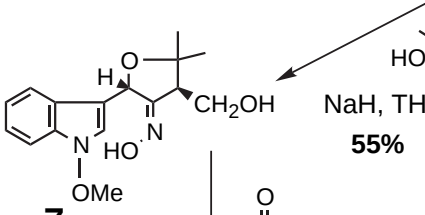
a) R^1=CHO; R^2, R^3=H
b) R^1= Ac; R^2, R^3=H
c) R^1=COOMe; R^2, R^3=H
d) R^1=CHO; R^2=H; R^3=NO_2
e) R^1 = CHO; R^2=I; R^3=H
f) R^1 = CHO; R^2=H; R^3=Br



5 + **4** **3** **6**

a) R^4 = ; **b**) R^4 =

a) Nu = OMe; **b**) Nu = O*n*-Pr; **c**) Nu = O ; **d**) Nu = O



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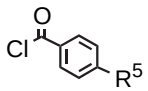
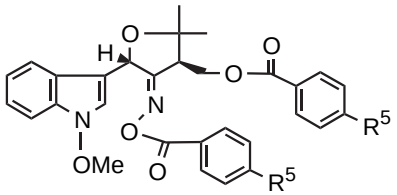




8

a) R^5 = Br; **b**) R^5 = Cl; **c**) R^5 = NO_2

Figure 1

ORTEP Drawing of 8c (*R* = 0 069)

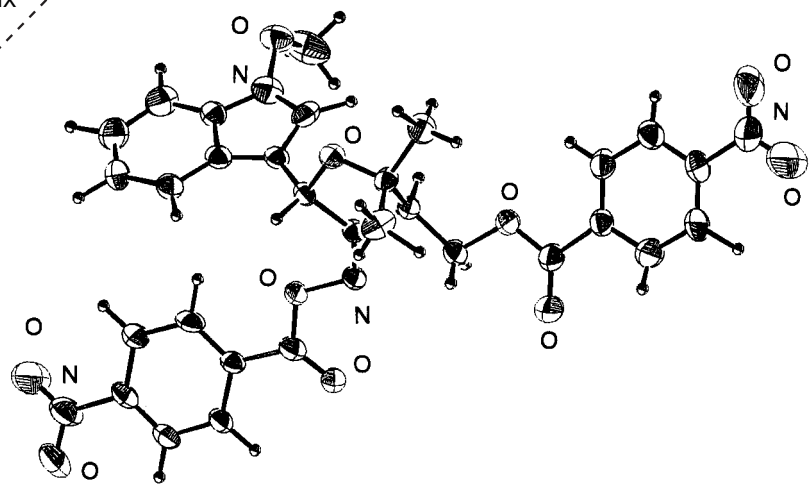
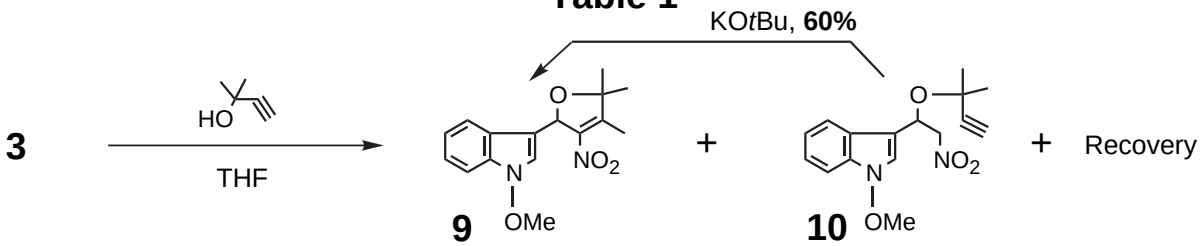


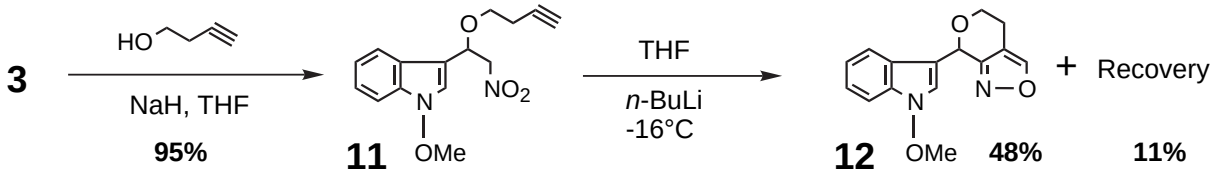
Table 1



9 **10**

Entry	Base (mol eq.)	Reaction Conditions Temp. (°C)	Time (min)	Yield (%) of **9**	**10**	Recovery
1	KO*t*Bu	rt	10	35	0	11
2	60% NaH	0	10	0	75	0

Scheme 2



cyclized product (**7**) was formed through the expected **6d**.

In order to determine its structure unequivocally by X-Ray single crystallographic analysis, an attempt was made to convert **7** to a crystalline compound. The reactions of *p*-bromo- and *p*-chlorobenzoyl chlorides with **7** afforded **8a** and **8b** in 63 and 82% yields, respectively, but they were not suitable crystals. *p*-Nitrobenzoyl chloride was finally found to give a 78% yield of **8c** as feasible prisms. Figure 1 shows ORTEP drawing of **8c**, and consequently the structure of **7** is proved as well.

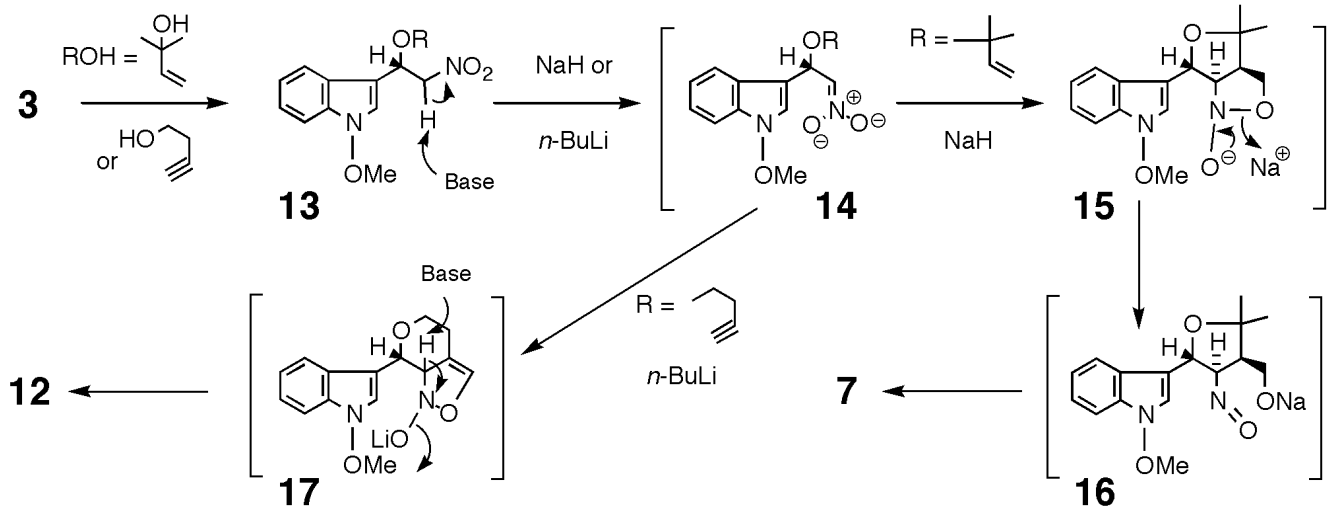
Taking the formation of **7** into consideration, we planned to produce novel 3-substituted 1-methoxyindoles in one pot by causing Michael addition to take place first, and then let the resultant product react intramolecularly by selecting an appropriate base. Employing KO*t*Bu as a base, the reaction of 1,1-dimethylpropargylalcohol with **3** in THF at room temperature provided a novel cyclized product (**9**) in 35% yield as shown in Table 1 (entry 1), while the same reaction using NaH in THF at 0℃ provided Michael addition product (**10**) in 75% yield (entry 2). Although the structure of **9** was determined based on its spectral data, further confirmation was obtained by the fact that **9** was produced in 60% yield from **10** by treatment with KO*t*Bu at 0℃ for 30 min.

Sodium 3-butyn-1-oxide also reacted with **3** in THF to give **11** in 95% yield (Scheme 2). By the treatment of **11** with *n*-BuLi in THF at –16°C, a novel cyclization occurred to give 7-(1-methoxyindol-3-yl)-4,5-dihydro-7*H*-pyrano[3,4-*c*]isoxazole (**12**) in 48% yield together with unreacted **11** (11%). Extension of this reaction to aromatic and aliphatic nitrovinyl compounds is in progress.

A possible reaction mechanism for the formations of **7** and **12** is shown in Scheme 3. Base abstracts active methylene proton of the Michael product (**13**), giving nitronate intermediate (**14**). In the case that the R substituent is 1,1-dimethylallyl group, cycloaddition[6] of nitronate to alkene side chain occurs to give **15**. Subsequent elimination of the alkoxy part[7] produces **7** *via* **16**. On the other hand, if the R substituent of **14** is 1,1-dimethylpropargyl group, cycloaddition of nitronate to alkyne side chain gives **17**. The following *n*-BuLi abstraction of hydrogen at the carbon attached to nitrogen with concomitant liberation of lithium hydroxide results in the formation of stable aromatic isoxazole (**12**).

In summary, we have disclosed that **3** has two reaction sites for nucleophilic substitution, and the choice

Scheme 3



of the solvent governs the position to which the nucleophiles add. In addition, Michael addition products (**6d**, **10**, and **11**) undergo interesting cyclizations depending on the bases giving novel 3-substituted 1-methoxyindoles (**7**, **9**, and **12**). Attempts to determine the scope and limitations of these reactions are in progress.

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