Nucleophilic substitution reactions of 1-methoxy-6-nitroindole-3-carbaldehyde 1

メタデータ	言語: English 出版者: 公開日: 2017-10-03 キーワード (Ja): キーワード (En): 作成者: Yamada, Koji, Yamada, Fumio, Shiraishi, Takei, Tomioka, Saori, Somei, Masanori メールアドレス: 所属:
URL	http://hdl.handle.net/2297/4373

NUCLEOPHILIC SUBSTITUTION REACTIONS OF 1-METHOXY-6-NITROINDOLE-3-CARBALDEHYDE [1]

Koji Yamada, Fumio Yamada, Takei Shiraishi, Saori Tomioka, and Masanori Somei*

Faculty of Pharmaceutical Sciences, Kanazawa University,
13-1 Takara-machi, Kanazawa 920-0934, Japan

Abstract — 1-Methoxy-6-nitroindole-3-carbaldehyde is proved to be a versatile substrate for the nucleophilic substitution reactions providing 2,3,6-trisubstituted indole derivatives. Preparation of a novel pyrimido[1,2-*a*]indole derivative is also reported.

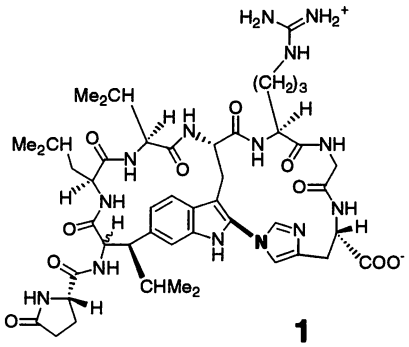
As natural products, there exist many biologically active peptides which contain tryptophan residue carrying either a C—N, C—S, or C—C bond at the 2 position, such as moroidin (**1**, Figure 1),[2a] phalloidin (**2**),[2b] etc.[2c] From the synthetic point of view, regioselective preparation of these bonds on indole nucleus in the later stage of synthesis is difficult in spite of various electrophilic substitution reactions are known. Our project to overcome the problem with a common method has led us to develop unprecedented nucleophilic substitution reactions on indole nucleus[1c,3] based upon our 1-hydroxyindole hypothesis.[4] Accordingly, 3-acyl-1-methoxyindoles (**3a**, **b**, **c**) and 1-methoxy-3-(2-nitrovinyl)indole (**3d**) are found to be good substrates for the synthesis of 2-substituted indoles (**4a**—**d**),[5] though the yield of products varies depending on the structure of nucleophiles and reaction conditions.

In this communication, we wish to report the reactivity characteristics of 1-methoxy-6-nitroindole-3-carbaldehyde (**3e**), which undergoes regioselective nucleophilic substitution reactions in better yield than those of **4a**—**d**, because the presence of an electron withdrawing nitro group increases the reactivity. What is better, the nitro group at the 6-position can be transformed into various functional groups, meeting our purposes to create our own method to synthesize **1**, **2**, and related natural products.

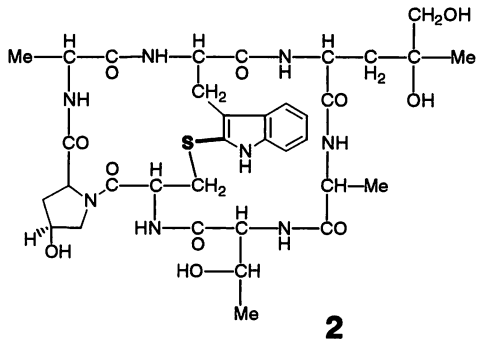
1-Methoxy-6-nitroindole (**6b**) was prepared from indoline (**5a**) in 70% overall yield through **5b** and **6a**, according to our previous synthetic method.[6] Subsequent Vilsmeier-Haack reaction of **6b** with $POCl_3$ and *N*,*N*-dimethylformamide (DMF) provided **3e**, an analog of "daikon phytoalexin,"[7] in 94% yield.

With **3e** in hand, dimethyl malonate was employed as a carbon-centered nucleophile to react with **3e** in the presence of KO*t*Bu in DMF at room temperature to give **7** in 92% yield. When 3-acetylpyridine was reacted with **3e** by the action of KH in THF, **8** was isolated in 92% yield. As a representative of sulfur-centered nucleophile, NaSMe was allowed to react with **3e** to result in the formation of **9** in 98% yield. Piperidine, as a nitrogen-centered nucleophile, reacted with **3e** in refluxing MeOH to afford **10** in 92% yield. Pyrrole and indole also provided **11** and **12** in 98 and 96% yields, respectively, by the reaction with **3e** using NaH as a base in DMF. Under similar reaction conditions, imidazole and

Figure 1

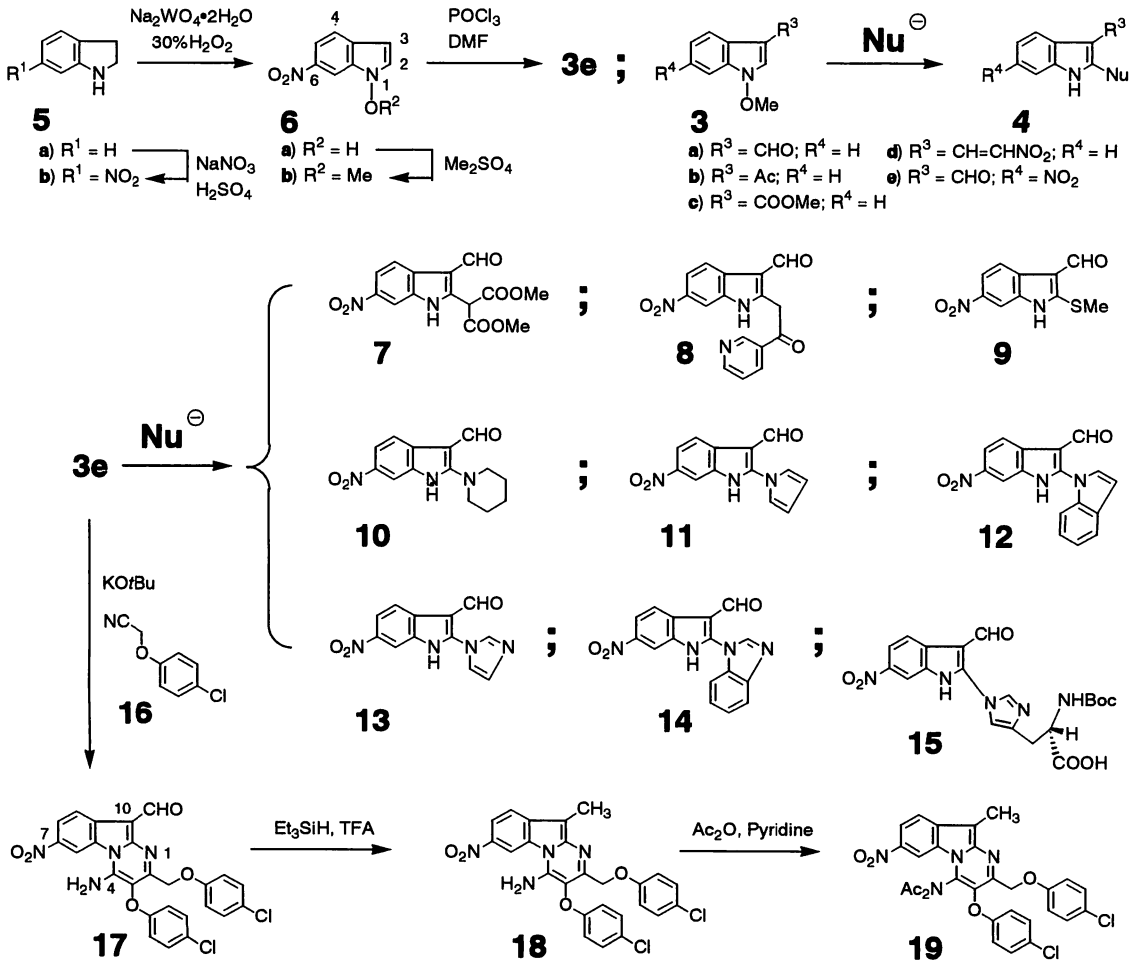


1



2

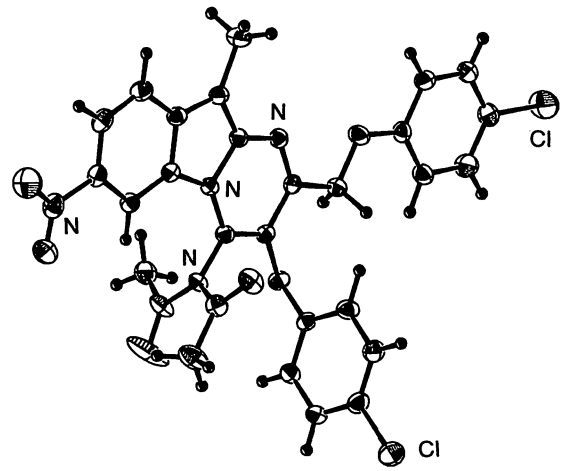
Scheme 1



benzimidazole reacted with **3e** to give **13** and **14** in 97 and 87% yields, respectively. Based on these successful results, α-*N*-*t*-Boc-L-histidine was allowed to react with **3e** in DMF by the action of NaH as a base, culminating in the formation of the desired **15** in 94% yield, which is a core structure of **1**. Thus, **3e** is proved to react with various types of nucleophiles in excellent yields, and a suitable substrate for preparing indoles having substituents at the 2-, 3-, and 6-positions, which are familiar substitution pattern often observed in the natural products.

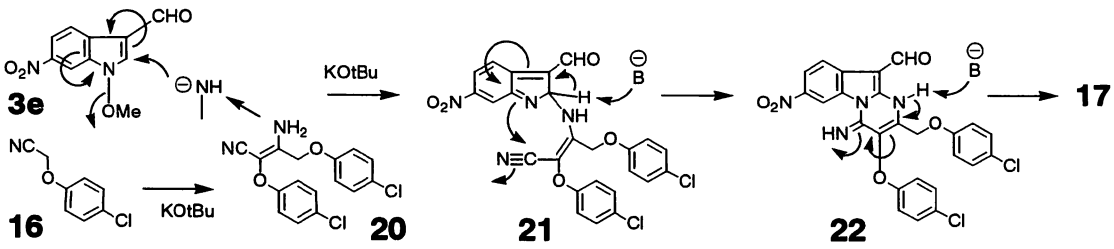
It is interesting to note that when the reaction of **3e** with *p*-chlorophenoxyacetonitrile (**16**) was carried out in the presence of KO*t*Bu in DMF at 0 °C, a novel 4-amino-3-*p*-chlorophenoxy-2-*p*-chlorophenoxymethyl-7-nitropyrimido[1,2-*a*]indole-10-carbaldehyde (**17**) was produced in 71% yield. The structure of pyrimido[1,2-*a*]indole skeleton was determined as follows. First, **17** was converted to 10-methyl compound (**18**) in 93% yield by the treatment with Et_3SiH in TFA at reflux. Then, **18** was reacted with Ac_2O-pyridine at room temperature to afford 89% yield of **19**. Luckily, **19** was suitable prisms for X-Ray single crystallographic analysis and its structure was determined unequivocally as shown in Figure 2.

Figure 2
ORTEP Drawing of **19**
(R = 0.045)



To clear the reaction mechanism for the formation of **17**, **16** was treated with KO*t*Bu in DMF at 0℃ in the absence of **3e**, and the result was a 41% yield of formation of **20** and recovery of **16**. Therefore, we can propose the following possible mechanism as shown in Scheme 2. As the methoxy group leaves from **3e**, the N anion of **20** generated from **16** by the action of KO*t*Bu attacks the 2-position of **3e** resulting in the formation of an intermediate (**21**). Base abstracts a proton from its 2-position, and the resultant anion of indole nitrogen attacks the cyano group on the side chain intramolecularly to afford **22**. Subsequent prototropy of imine group completes the formation of **17**. The other possibility is an addition-elimination mechanism. Extention of this finding to the new heterocycles is currently under investigation.

Scheme 2



In conclusion, we have demonstrated that **3e** is an excellent substrate for obtaining 2,3,6-trisubstituted

indole derivatives. Application of this methodology to natural products synthesis, based on the regio-selective nucleophilic substitution reaction, is in progress.

REFERENCES AND NOTES

1. a) Dedicated to the 70th birthday of Prof. A. I. Meyers. b) This is Part 113 of a series entitled "The Chemistry of Indoles". c) Part 112: T. Hayashi, W. Peng, Y. Nakai, K. Yamada, and M. Somei, *Heterocycles*, 2002, **57**, 421. All new compounds gave satisfactory spectral and elemental analysis or high-resolution MS spectral data for crystals or oil, respectively. **3e**, mp 180— 182 ℃; **7**, mp >300 ℃; **8**, mp >300 ℃; **9**, mp >300 ℃; **10**, mp >300 ℃; **11**, mp >300 ℃; **12**, mp 291—293 ℃; **13**, mp 268—272 ℃; **14**, mp >300 ℃; **15**, mp 125—136 ℃ (decomp); **17**, mp 242— 244 ℃; **18**, mp 240—241 ℃ (decomp); **19**, mp 217—219 °C (decomp).
2. a) T. -W. C. Leung, D. H. Williams, J. C. J. Barna, and S. Foti, *Tetrahedron*, 1986, **42**, 3333; S. D. Kahn, P. M. Booth, J. P. Waltho, and D. H. Williams, *J. Org. Chem.*, 1989, **54**, 1901; *idem.*, *ibid.*, 2000, **65**, 8406. b) F. Lynen and U. Wieland, *Liebigs Ann. Chem.*, 1938, **548**, 1938; L. Falcigno, S. Costantini, G. D'Auria, B. M. Bruno, S. Zobeley, G. Zanotti, and L. Paolillo, *Chem. Eur. J.*, 2001, **7**, 4665 and references cited therein. c) J. Kobayashi, H. Suzuki, K. Shimbo, K. Takeya, and H. Morita, *J. Org. Chem.*, 2001, **66**, 6626; M. Mure and K. Tanizawa, *Biosci. Biotech. Biochem.*, 1997, **61**, 410 and references cited therein.
3. M. Somei, H. Morikawa, K. Yamada, and F. Yamada, *Heterocycles*, 1998, **48**, 1117; J. A. Joule, "Progress in Heterocyclic Chemistry", Vol. 11, ed. by G. W. Gribble and T. L. Gilchrist, Elsevier Science Ltd., Oxford, 1999, pp. 45—65; M. Hasegawa, K. Yamada, Y. Nagahama, and M. Somei, *Heterocycles*, 1999, **51**, 2815. See also references, 4 and 5.
4. Review; M. Somei, *J. Synth. Org. Chem. Jpn.*, 1991, **49**, 205; M. Somei, T. Kawasaki, Y. Fukui, F. Yamada, T. Kobayashi, H. Aoyama, and D. Shinmyo, *Heterocycles*, 1992, **34**, 1877; M. Somei and Y. Fukui, *ibid.*, 1993, **36**, 1859; M. Hasegawa, M. Tabata, K. Satoh, F. Yamada, and M. Somei, *ibid.*, 1996, **43**, 2333; Review: M. Somei, *ibid.*, 1999, **50**, 1157. See also reference 6b.
5. F. Yamada, Y. Fukui, D. Shinmyo, and M. Somei, *Heterocycles*, 1993, **35**, 99; F. Yamada, D. Shinmyo, and M. Somei, *ibid.*, 1994, **38**, 273; M. Somei, F. Yamada, T. Izumi, and M. Nakajou, *ibid.*, 1997, **45**, 2327; M. Somei, M. Nakajou, T. Teramoto, A. Tanimoto, and F. Yamada, *ibid.*, 1999, **51**, 1949; M. Somei, A. Tanimoto, H. Orita, F. Yamada, and T. Ohta, *ibid.*, 2001, **54**, 425.
6. a) M. Somei and T. Kawasaki, *Heterocycles*, 1989, **29**, 1251. b) K. Yamada, T. Kawasaki, T. Fujita, and M. Somei, *ibid.*, 2001, **55**, 1151.
7. a) J. Kinjo, K. Yokomizo, Y. Awata, M. Shibata, and T. Nohara, Symposium Papers, 29th Symposium on the Chemistry of Natural Products, Sapporo, August 1987, p. 628. b) R. M. Acheson, P. G. Hunt, D. M. Littlewood, B. A. Murrer, and H. E. Rosenberg, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1117; M. Somei, H. Ohnishi, and Y. Shoken, *Chem. Pharm. Bull.*, 1986, **34**, 677. See also reference 6a.

Received, 1st March, 2002