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Unusual Cyclization and *SN'*-Type Displacement of Carbazole Sulfoxide under Pummerer Reaction Conditions

Tomomi Kawasaki, Hirohide Suzuki, Ikuhiro Sakata, Hiroyuki Nakanishi, and Masanori Sakamoto*

Meiji College of Pharmacy, 1-35-23 Nozawa, Setagaya-ku, Tokyo 154, Japan

Abstract: Trifluoroacetic anhydride induced Pummerer reactions of carbazole-sulfoxide **1** follow an unusual pathway, in which the initially formed acyloxysulfonium salt **3** undergoes not the usual abstract of α-proton but internal nucleophilic substitution with the indole nuclear followed by SN'-type reaction of an intermediate **4** with additive nucleophiles to give 1-substituted carbazole sulfides **2**.
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The Pummerer cyclization provides a versatile method for the construction of frameworks in natural product synthesis,[1] especially indole alkaloids.[2] The generally accepted mechanism for the cyclization involves activation of the sulfoxide by converting the oxygen atom into a leaving group by *O*-acylation, thereby generating acyloxysulfonium salt followed by abstraction of α-proton with elimination of the acyloxy group forming thionium ion, and the subsequent trapping reaction with internal nucleophile.[1] In spite of its general applicability, several unusual Pummerer cyclizations have recently been reported.[3] These processes include attack of an internal nucleophile on sulfur atom of the initially formed acyloxysulfonium salt, in preference to generation of a thionium ion; this gives a new tricoordinate sulfur species, which undergoes subsequent reactions such as substitution at α-site of sulfur[3] and β-elimination.[4] However, these unusual reactions have contributed little to any generally useful synthetic method.[3f]

In the context of our studies[5] on the synthesis of aspidosperma and strychnos-type ring system by Pummerer cyclization constructing the E ring, we have found an unusual route of Pummerer reaction of carbazole sulfoxide **1** under standard Pummerer reaction conditions in the presence of several nucleophiles to give the corresponding 1-substituted carbazole sulfides **2**. This reaction includes the nucleophilic displacement of acyloxy group by the indole ring in the initially formed acyloxysulfonium intermediate **3**

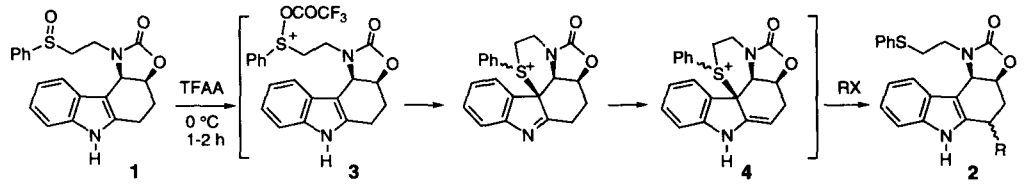

Table 1. Reaction of Sulfoxide **1** with TFAA in the Presence of Nucleophiles

Entry	RX	R	Product	Yield (%) [α : β]	
1	HOMe	OMe	**2a**	72	[3 : 4]
2	HOEt	OEt	**2b**	74	[2 : 1]
3	Me_3SiN_3	N_3	**2c**	72	[3 : 4]
4	$HSCH_2Ph$	SCH_2Ph	**2d**	80	[1 : 1]
5	BrMgMe	Me	**2e**	70	[6.5 : 1]

and subsequent *SN'*-type reaction of a tricoordinate sulfur intermediate **4**[6] with additive nucleophiles. Thus, sulfoxide **1** was treated with trifluoroacetic anhydride (TFAA) in 1,2-dichloroethane at 0 ℃ for 15 min, followed by addition of methanol (50 eq) to give a mixture of α- and β-isomers (3 : 4) of 1-methoxy-carbazole sulfide **2a** [7] (72 %). A similar procedure applied to N-, S-, and C-nucleophiles instead of O-nucleophile afforded the corresponding 1-substituted carbazole sulfides **2b-e** in good yields as shown in **Table 1**. The nonstereoselectivity of the reactions using non-ionic reagents is caused by *SN*1'-type reaction (entries 1-4), while the reaction using Grignard reagent underwent stereoselectively *SN*2'-type reaction to give α-isomer **2e** predominantly (entry 5). We are currently investigating the full scope and limits of reaction of this type, which could represent a useful synthetic method.

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5. We have recently found that trifluoroacetic anhydride induced normal Pummerer cyclization of *N*-acetyl derivative of **1**, which successfully constructed the E ring of these alkaloids. This normal cyclization and synthesis of these alkaloids will be reported in the near furture.
6. The intermediate **4** (a mixture of diastreoisomers) was identified by ^{1}H-NMR data (δ 6.05 and 6.1 ppm; vinyl protons) of the reaction mixture in $CDCl_3$.
7. All new compounds were characterized by ^{1}H-NMR, IR, and MS data and gave satisfactory analytical and/or high resolution MS data. Their stereochemistries were confirmed by NOE experiments.

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