Remarkably Mild and Efficient Cetrimonium Bromide Catalyzed Friedel–Crafts Amidoalkylation of Sesamols with *N*-Boc Imines Generated In Situ in Aqueous Medium

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Abstract: A remarkably mild and efficient cetrimonium bromide (CTAB) catalyzed Friedel–Crafts amidoalkylation of sesamol or its 2-substituted derivatives with *N*-Boc imines generated in situ was developed. A wide range of 6-amidoalkyl sesamols were synthesized in high yields. This methodology was also applicable to 2-naphthols.

Key words: sesamol, Friedel–Crafts amidoalkylation, α-amido sulfones, CTAB, 6-amidoalkyl sesamols

The Friedel–Crafts aminoalkylation or amidoalkylation of electron-rich phenols with imines represents an important transformation for the synthesis of biologically active compounds and chiral amino alcohol ligands. For example, synthesis of 1-aminoalkyl naphthols via Friedel–Crafts amino- or amidoalkylation of 2-naphthols attracted much attention due to the importance of the products.[1]

Sesamol is one of the representative structural motifs often observed in natural alkaloids and biologically active compounds.[2] As an electron-rich phenol, sesamol and its derivatives are good nucleophiles that can be employed in the Friedel–Crafts reaction to construct complex natural products.[3] Jurd has reported the Mannich type Friedel–Crafts aminoalkylation of sesamol and the application of the resulting Mannich bases in the synthesis of anti-tumor agents.[4] Recently, Frackenpohl also reported the same reaction and its application in the synthesis of insecticidal heterolignans.[5] However, to the best of our knowledge, a systematic study on Friedel–Crafts amidoalkylation of sesamol with imines has not been reported.

N-Boc imines are of great importance in nucleophilic addition because they are very reactive electrophiles and the Boc group can be easily removed from the resulting adducts, however, *N*-Boc imines are known to be unstable and difficult to handle. Gratifyingly, this problem can be circumvented by generating *N*-Boc imines in situ from stable α-amido sulfones.[6] Herein, we report a remarkably mild and efficient Friedel–Crafts amidoalkylation of sesamol or its 2-substituted derivatives with *N*-Boc imines generated in situ, through which a wide variety of 6-amidoalkyl sesamols were synthesized in high yields.

First, we investigated the Friedel–Crafts amidoalkylation of sesamol **1a** with *N*-Boc imine generated in situ from α-amido sulfone **2a** in water at 30 °C, employing 1.5 equivalents of CsOH as the base (Table 1, entry 1). The reaction proceeded in two days to afford 64% of the desired product 6-amidoalkyl sesamol **3a**. Encouraged by this finding, we next examined the effects of various bases. Among these bases, Na_2CO_3 gave a promising yield of 80%. However, no increase in yield was observed by prolonging the reaction time to three days (Table 1, entry 10). When the reaction was performed at higher temperature, many side products arose and the yield dropped significantly (Table 1, entry 11).

Recently, Kobayashi and other groups reported several surfactant-promoted reactions in aqueous medium.[7] Therefore, in order to improve the efficiency of this reaction, we introduced surfactants into the reaction mixture. To our delight, several surfactants accelerated the reaction dramatically. In the presence of 10 mol% of surfactants SDS (sodium 1-dodecanesulfonate) and 12-2-12 [ethanediyl-1,2-bis(dodecyldimethyl-ammonium bromide)], the reaction proceeded smoothly to afford more than 80% yield of the product in five hours (Table 1, entries 12 and 13). Moreover, 10 mol% of CTAB (cetrimonium bromide) provided almost quantitative amounts of product in five hours (Table 1, entry 14). Further research indicated that the reaction was actually complete within only three hours (Table 1, entry 15). However, reducing the catalyst loading to 5 mol% resulted in an obvious decrease of product yield (Table 1, entry 16).

Having established the optimal reaction conditions, the generality of this reaction was examined. In the presence of 10 mol% of CTAB, sesamol or its 2-substituted derivatives underwent Friedel–Crafts amidoalkylation with a wide variety of α-amido sulfones in water at 30 °C.[8,9] The results are summarized in Table 2.

As can be seen in Table 2, it is clear that the methodology is quite general. All aryl or alkyl α-amido sulfones tested underwent the reaction smoothly to provide the corresponding 6-amidoalkyl sesamols in good yields. For aryl α-amido sulfones, the substituents on the aromatic rings

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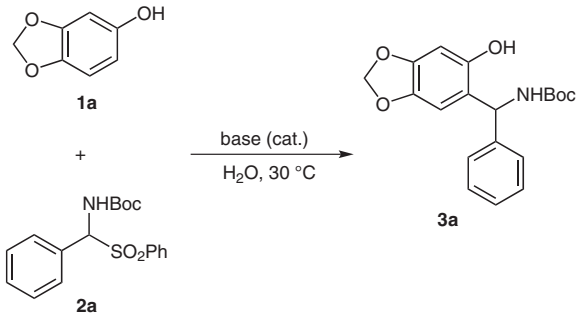
Table 1 Screening of Bases and Catalysts in the Friedel–Crafts Amidoalkylation of Sesamol **1a** with α-Amido Sulfone **2a**[a]

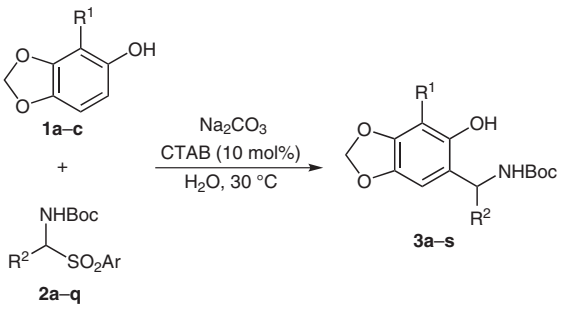


Entry	Base	Catalyst (mol%)	Time (h)	Yield (%)[b]
1	$CsOH·H_2O$	none	48	64
2	KOH	none	48	76
3	NaOH	none	48	51
4	$LiOH·H_2O$	none	48	66
5	Cs_2CO_3	none	48	73
6	K_2CO_3	none	48	61
7	Na_2CO_3	none	48	80
8	Na_3PO_4	none	48	73
9	NaOAc	none	48	33
10	Na_2CO_3	none	72	79
11[c]	Na_2CO_3	none	48	70
12	Na_2CO_3	SDS (10)	5	82
13	Na_2CO_3	12-2-12 (10)	5	84
14	Na_2CO_3	CTAB (10)	5	97
15	Na_2CO_3	CTAB (10)	3	97
16	Na_2CO_3	CTAB (5)	5	67

[a] Unless indicated otherwise, the reaction was conducted with sesamol **1a** (0.24 mmol), α-amido sulfone **2a** (0.2 mmol) and base (0.3 mmol) in H_2O (2.0 mL) with or without catalyst at 30 °C.
[b] Isolated yield.
[c] The reaction was performed at 50 °C.

affected the reaction rate to some degree. The reactions of aryl α-amido sulfones bearing electron-donating groups on the *para*-positions completed within only three hours (Table 2, entries 2 and 4), while reactions of aryl α-amido sulfones bearing electron-withdrawing groups on the *para*-positions proceeded slower (Table 2, entries 6, 8 and 9). Prolonged reaction time was needed for aryl α-amido sulfones bearing *meta*- or *ortho*-substituents on the aromatic rings (Table 2, entries 3, 5, 7, and 10–12). In addition, electron-withdrawing substituents on the *meta* and *ortho* positions of the aromatic rings retarded the rate and the reaction required to ten hours to complete (Table 2, entries 7, and 10–12). 1-Naphthyl and heteroaromatic α-amidosulfones provided the corresponding products in

Table 2 Friedel–Crafts Amidoalkylation of Sesamol **1** with α-Amido Sulfone **2** Catalyzed by CTAB[a]



Entry	**1** (R^1)	**2** (R^2)	Time (h)	Yield (%)[b]
1	**1a** (H)	**2a** (Ph)	3	97
2	**1a** (H)	**2b** (4-MeC_6H_4)	3	95
3	**1a** (H)	**2c** (3-MeC_6H_4)	5	90
4	**1a** (H)	**2d** (4-$MeOC_6H_4$)	3	91
5	**1a** (H)	**2e** (2-$MeOC_6H_4$)	5	85
6	**1a** (H)	**2f** (4-FC_6H_4)	5	95
7	**1a** (H)	**2g** (3-FC_6H_4)	10	91
8	**1a** (H)	**2h** (4-ClC_6H_4)	5	92
9	**1a** (H)	**2i** (4-BrC_6H_4)	5	96
10	**1a** (H)	**2j** (3-BrC_6H_4)	10	97
11	**1a** (H)	**2k** (2-BrC_6H_4)	10	90
12	**1a** (H)	**2l** (3-$F_3CC_6H_4$)	10	88
13	**1a** (H)	**2m** (1-Naph)	5	94
14	**1a** (H)	**2n** (2-furyl)	5	91
15	**1a** (H)	**2o** (2- thienyl)	3	85
16[c]	**1a** (H)	**2p** (*i*-Pr)	5	93
17	**1a** (H)	**2q** (*c*-C_6H_{11})	5	95
18	**1b**(Me)	**2a** (Ph)	30	83
19	**1c** (I)	**2a** (Ph)	16	95

[a] Unless indicated otherwise, the reaction was conducted with sesamol **1** (0.24 mmol), α-amido sulfone **2** (0.2 mmol) and Na_2CO_3 (0.3 mmol) in H_2O (2.0 mL) with CTAB (10 mol%) at 30 °C. Ar = Ph.
[b] Isolated yield.
[c] Ar = 4-MeC_6H_4

high yields within five hours (Table 2, entries 13–15). It is noteworthy that even alkyl α-amidosulfones underwent the reaction smoothly to afford excellent yields of the products (Table 2, entries 16 and 17). In addition, 2-methyl sesamol and 2-iodo sesamol reacted with *N*-Boc imine generated in situ from α-amido sulfone **2a** to give the products in good yields after an extended reaction time (Table 2, entries 18 and 19).

Furthermore, when several naphthols were also subjected to the CTAB-catalyzed Friedel–Crafts amidoalkylation with imines generated in situ from α-amido sulfone **2a** under the optimized reaction conditions, both 2-naphthol and 6-bromo-2-naphthol underwent the reaction rapidly to generate the corresponding products **3t** and **3u** in high yields (Figure 1). However, the reaction of 1-naphthol proceeded sluggishly to provide the product **3v** in poor yield.

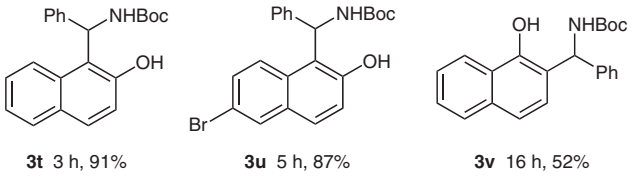


Figure 1 Products of Friedel–Crafts amidoalkylation of naphthols with *N*-Boc imine generated in situ from α-amido sulfone **1a**

In conclusion, we have developed a remarkably mild and efficient CTAB-catalyzed Friedel–Crafts amidoalkylation of sesamol or its 2-substituted derivatives with *N*-Boc imines generated in situ. A wide range of 6-amidoalkyl sesamols were synthesized in high yields through this transformation. This methodology was also appropriate for 2-naphthols.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(8) **Friedel–Crafts Amidoalkylation; General Procedure:** *N*-Boc α-amido sulfone (0.2 mmol, 1.0 equiv), Na_2CO_3 (0.3 mmol, 1.5 equiv), CTAB (0.02 mmol, 10%) and H_2O (2 mL) were added to a 10-mL glass vial equipped with a small magnetic stirring bar. Sesamol (0.24 mmol, 1.2 equiv) was added and, after stirring for the stipulated time at 30 °C, the mixture was diluted with H_2O (3 mL) and extracted with Et_2O (3 × 25 mL). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel flash chromatography (EtOAc–Hexanes, 1:10) to give the pure product.

(9) ***Tert*-butyl (6-Hydroxybenzo[d][1,3]dioxol-5-yl)(phenyl)-methylcarbamate (3a):** Yield: 97%; white solid; mp 168.5–168.9 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.31 (s, 1 H), 7.61 (d, *J* = 9.6 Hz, 1 H), 7.29–7.22 (m, 4 H), 7.19–7.14 (m, 1 H), 6.92 (s, 1 H), 6.42 (s, 1 H), 6.11 (d, *J* = 9.6 Hz, 1 H), 5.88 (s, *J* = 0.6 Hz, 1 H), 5.84 (s, *J* = 0.6 Hz, 1 H), 1.39 (s, 9 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 154.99, 148.49, 146.09, 143.67, 139.83, 128.03, 126.63, 126.36, 121.09, 107.39, 100.60, 97.39, 77.99, 51.21, 28.28; HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{19}H_{21}NNaO_5$: 366.1317; found: 366.1312

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