ORGANIC LETTERS

2002
Vol. 4, No. 3
459−461

The First Intermolecular Friedel–Crafts Acylation with β-Lactams

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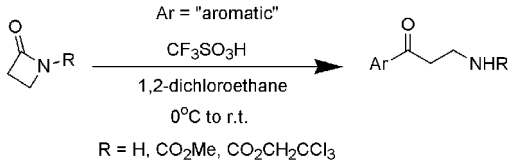
Received December 11, 2001

ABSTRACT



The first intermolecular Friedel–Crafts acylation of a variety of aromatic substrates with azetidinones is described. The Friedel–Crafts acylations are performed under very mild conditions, using trifluoromethanesulfonic acid to produce β-amino aromatic ketones in excellent yields.

Friedel−Crafts reactions are among the most common and important transformations in organic chemistry for electrophilic aromatic alkylations and acylations.[1] A significant number of Lewis acid catalysts, including $AlCl_3$, $SnCl_4$, and $BF_3{\cdot}OEt_2$ have been shown to be very successful for the acylation of aromatic substrates with acid chlorides or anhydrides.[2] Surprisingly, to our knowledge, no intermolecular Friedel−Crafts acylations utilizing β-lactams as substrates have been reported to date. The highly strained β-lactam was anticipated to be a good substrate for acylating aromatics to produce β-amino aromatic ketone derivatives. Considering the proven generality and usefulness of Friedel−Crafts acylations in organic synthesis, as well as the easy access to a wide range of substituted β-lactams, we herein report a significant expansion of the arsenal of Friedel−Crafts reactions with the use of azetidinones as substrates (Figure 1).

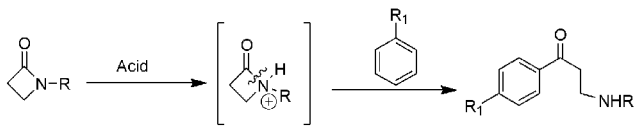


Figure 1. Intermolecular Friedel−Crafts acylation with azetidinones.

Recently, it was reported that aromatic esters can be activated with trifluoromethanesulfonic acid, which upon reaction with various aromatic compounds (both electron-rich and electron-poor) produced benzophenone derivatives in good yields.[3] In light of these results, we envisioned that under similar superacid activating conditions the strained β-lactam was anticipated to be a good substrate for acylating aromatics to produce the β-amino aromatic ketone derivatives. Herein we report a very mild procedure for the acylation of aromatic substrates with 2-azetidinones and *N*-substituted azetidinones with trifluoromethanesulfonic acid to give the corresponding β-amino aromatic ketones in good to excellent yields (Table 1).

The efficacy of 2-azetidinone as a Friedel−Crafts substrate for a variety of aromatic compounds, including toluene, chlorobenzene, anisole, and nitrobenzene, is illustrated in Table 1. With the exception of nitrobenzene, all reactions provided the β-amino aromatic ketone derivatives **2** as the triflate salt in excellent yields (Table 1). By contrast, the less strained β-butyrolactam **3** failed to undergo the Friedel−

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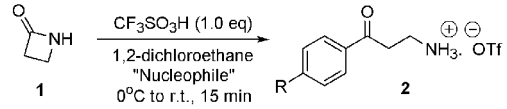
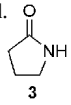
10.1021/ol010291w CCC: $22.00
Published on Web 01/03/2002

Table 1. Friedel−Crafts Acylation with Trifluoromethanesulfonic Acid on Various Aromatic Substrates



substrate **1**	R	nucleophile	yield (%) of **2**
1	H	benzene	98
1	Me	toluene	93
1	Cl	chlorobenzene	92
1	MeO	anisole	95
1[a]	Br	bromobenzene	92
1	NO_2	nitrobenezene	0
3[b]	H	benzene	0

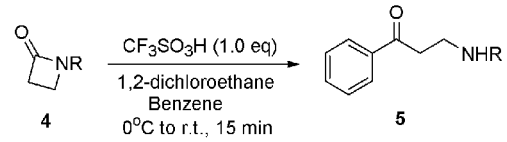
[a] Optimal yields obtained when heated to 80 °C for 2 h. [b] Reaction was heated to reflux in benzene with no desired product isolated.



Crafts reaction even under more vigorous conditions. A possible mechanism consistent with previous reported studies could involve *N*-protonation of the *β*-lactam, followed by C−N bond fission resulting in the relief of ring strain.[4] The highly reactive acyl carbonium ion then further reacts with the aromatic substrate, providing the acylated product (Figure 1).

The Friedel−Crafts acylation of various *N*-acylated 2-azetidinones **4** with benzene in 1,2-dichloroethane was subsequently investigated (Table 2). Treatment of 2-azetidinone

Table 2. Friedel−Crafts Acylation with Trifluoromethanesulfonic Acid



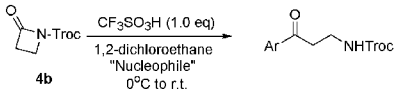
substrate **4**	R	acid	yield (%) of **5**
4a	CO_2Me	CF_3SO_3H	65
4b	$CO_2CH_2CCl_3$	CF_3SO_3H	85
4b	$CO_2CH_2CCl_3$	$AlCl_3$	np[a]
4b	$CO_2CH_2CCl_3$	$BF_3{\cdot}OEt_2$	np[a]
4b	$CO_2CH_2CCl_3$	$SnCl_4$	np[a]

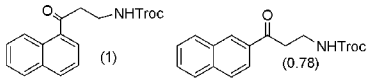
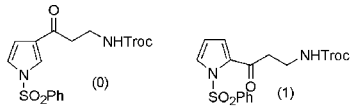
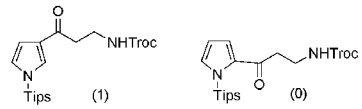
[a] No products isolated.

4a or **4b** with 1.0 equiv of trifluoromethanesulfonic acid at 0 °C in a 1:1 mixture of benzene and 1,2-dichloroethane provided the corresponding products **5** in good yields. Treatment of the 2-azetidinones **4b** with traditional Lewis acids did not result in any Friedel−Crafts acylation of benzene.

Treatment of the *N*-Troc (2,2,2-trichloroethoxycarbonyl)-protected *β*-lactam **4b** with 1.1 equiv of trifluoromethanesulfonic acid at 0 °C in the presence of an excess of naphthalene (10 equiv) for 15 min at 0 °C provided a 1:0.78 mixture of the 1- and 2-substituted naphthalene isomers in good yields (Table 3). The *β*-lactams also proved to be

Table 3. Friedel−Crafts Acylation of Naphthalene and Pyrroles



nucleophile	Products	% yield
		84%[a]
		65%
		35%

[a] Isolated as an inseparable mixture of 1- and 2-substituted naphthalene derivatives.

substrates for the acylation of aromatic heterocycles, illustrated here with the phenylsulfonyl- and triisopropyl-protected pyrroles (Table 3). The phenylsulfonyl- and the silyl-protected pyrroles provided the 2- and 3-acylated substrates, respectively.

In addition, we examined the *N*-aryl 2-azetidinones (*p*-NO_2, *p*-Cl, *p*-F, H, *p*-OMe) **6a**−**e** under the same mild condition because of their high propensity to suffer CO−N bond cleavage under both acidic and basic conditions.[5] The *N*-aryl 2-azetidinones were prepared by standard protocols.[6] *N*-Aryl 2-azetidinones have previously been shown to undergo a Fries-type rearrangement, resulting in the corresponding 2,3-dihydro-4(1*H*)-quinolones **7** under forcing conditions (reflux in trifluoroacetic acid for 2 h).[7] We report here a significantly milder method for the preparation of quinolones **7** by trifluoromethanesulfonic acid (1.0 equiv)

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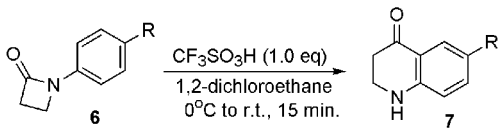
(7) (a) Kano, S.; Ebata, T.; Shibuya, S. *Heterocycles* **1976**, *4*(10), 1649. (b) Kano, S.; Ebata, T.; Shibuya, S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2105. (c) Kano, S.; Shibuya, S.; Ebata, T. *Heterocycles* **1981**, 15(2), 1011.

Table 4. Fries-Type Rearrangement of Aryl β-Lactams



substrate **6**	R	time	yield (%) of **7**
6a	NO_2	15 min	0
6b	Cl	15 min	97
6c	F	15 min	98
6d[a]	H	15 min	96
6e[a]	OMe	15 min	97

[a] Two equivalents of trifluoromethanesulfonic acid were required for optimal yields.

in 1,2-dichloroethane (0 °C to room temperature over 15 min) in excellent yields (Table 4).

In summary, we report the first Friedel−Crafts acylations of aromatic substrates using β-lactams with trifluoromethanesulfonic acid. Further studies of this methodology and the potential applications to the total synthesis of natural products are currently under investigation in these laboratories and will be reported in due course.

Acknowledgment. The authors gratefully acknowledge the financial support provided by the Petroleum Research Fund, administered by the American Chemical Society, and Michigan State University.

Supporting Information Available: Experimental procedures and IR, ^{1}H and ^{13}C NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL010291W