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Efficient [3,3]-sigmatropic rearrangement accelerated by a trifluoroacetyl group: synthesis of benzofurans under mild conditions

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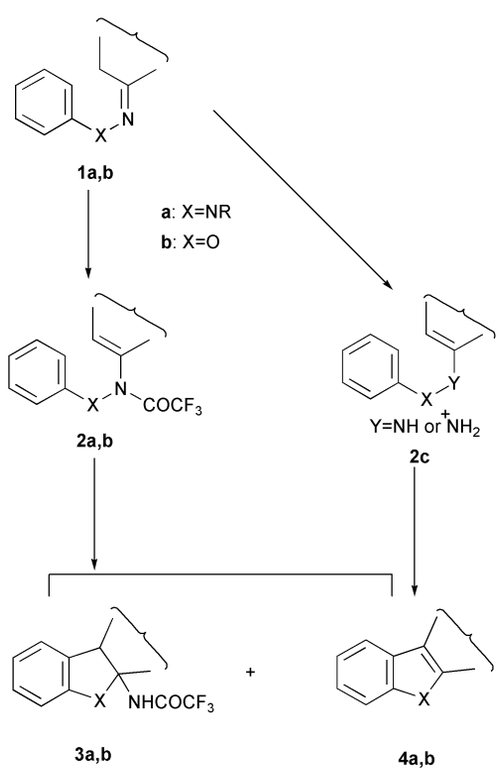
The [3,3]-sigmatropic rearrangement took place smoothly during the course of trifluoroacetylation of *O*-phenyloxime at below room temperature to give the dihydrobenzofuran or benzofuran as a result of concomitant cyclization.

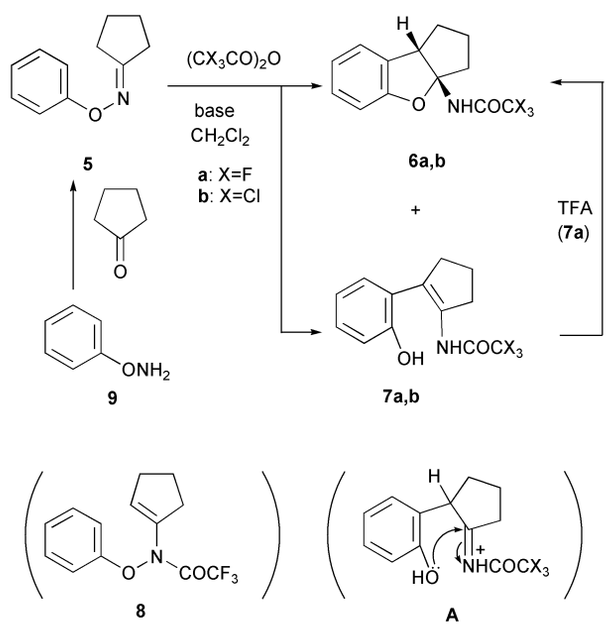
[3,3]-Sigmatropic rearrangement is one of the most reliable methods for the formation of carbon–carbon bonds in organic synthesis. Although it has been widely used, harsh conditions are generally required for successful rearrangement. In the case of compound **1** having an imine moiety, either acid catalyst or high temperature is required for successful rearrangement to form cyclized heterocycles *via* **2c** as exemplified in the Fischer indolization.[1] In order to solve these problems in the synthesis of indole and related compounds, we have recently found a novel [3,3]-sigmatropic rearrangement of enehydrazine **2a** having a trifluoroacetyl group which proceeds smoothly under non-acidic mild conditions to give indolines **3a** or indoles **4a** in good yields (Scheme 1).[2] Our studies show that the [3,3]-sigmatropic rearrangement of enehydrazines is accelerated by a trifluoroacetyl group.



Scheme 1

On the basis of these results, we investigated [3,3]-sigmatropic rearrangement of *N*-trifluoroacetyl enehydroxylamine **2b** and established a new and efficient synthesis of dihydrobenzofuran **3b** and benzofuran **4b**. This newly developed rearrangement proceeded even between 0 °C and rt to give dihydrobenzofuran **3b** or benzofuran **4b**. Conversion of oxime ether **1b** into benzofuran **4b** had previously been reported,[3] requiring reaction conditions using both acid catalysis and elevated temperature such as refluxing ethanol.

According to the reaction conditions employed in the related hydrazone **1a**, we first examined trifluoroacetylation of oxime ether **5** which was readily prepared by condensation of cyclopentanone with *O*-phenylhydroxylamine **9**[4] (Scheme 2, Table 1).



Scheme 2

Treatment of oxime ether **5** with trifluoroacetic anhydride (TFAA) (1 equiv.) in the presence of Et_3N (1.5 equiv.) at 0 °C gave the phenol **7a** in low yield which would be formed *via* [3,3]-sigmatropic rearrangement of a transiently formed intermediate of *N*-trifluoroacetyl hydroxylamine **8** (entry 1). Interestingly, acylation of **5** with TFAA in the absence of a base even at 0 °C gave *cis*-dihydrobenzofuran **6a** as a sole product without the isolation of enehydroxylamine **8** (entry 2). When trichloroacetic anhydride (TCAA) was used as an acylating reagent, the reaction proceeded in boiling CH_2Cl_2 to give dihydrofuran **6b** in good yield (entry 3). On the other hand, the use of Ac_2O was ineffective for the synthesis of benzofuran. Thus, in the case of the reaction with Ac_2O in boiling CH_2Cl_2, the starting material **5** was completely recovered and the reaction with Ac_2O at 140 °C in refluxing xylene gave many spots on TLC due to the formation of a complex reaction mixture. The phenol **7a** was readily converted into **6a** by treatment with TFA. The enamine part in

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Table 1 Acylation and rearrangement of *O*-phenyloxime ether **5**

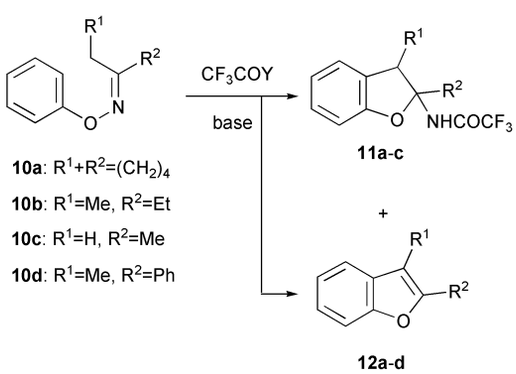
Entry	$(CX_3CO)_2O$ (eq.)	Base (eq.)	Temp./°C	Time/h	Yield (%) **6**	Yield (%) **7**
1	TFAA (1)	Et_3N (1.5)	0	4	—	8
2	TFAA (1)	—	0	3	99	—
3	TCAA (1)	—	40	5	94	—

Table 2 Acylation and rearrangement of *O*-phenyloxime ethers **10**

Entry	Substrate	Y	Base	Solvent	Temp./°C	Time/h	Yield (%) **11**	Yield (%) **12**
1	**10a**	$OCOCF_3$	—	CH_2Cl_2	0	23	94	—
2	**10a**	OSO_2CF_3	Et_3N	CH_2Cl_2	rt	5	—	85
3	**10b**	$OCOCF_3$	—	MeCN	80	5	64	—
4	**10b**	OSO_2CF_3	Et_3N	CH_2Cl_2	rt	4	—	80
5	**10c**	$OCOCF_3$	—	MeCN	80	4	82	—
6	**10c**	OSO_2CF_3	Et_3N	CH_2Cl_2	rt	1	—	81
7	**10d**	$OCOCF_3$	—	MeCN	80	20	—	—
8	**10d**	OSO_2CF_3	DMAP	CH_2Cl_2	rt	2.5	—	83

phenol **7** was protonated by TFA to form the iminium **A** which was immediately subjected to cyclization to give the dihydrobenzofuran **6a**. In the acylation of oxime ether **5** with TFAA in the presence of Et_3N (entry 1, Table 1), TFA formed was immediately trapped as the corresponding salt. Therefore, the dihydrobenzofuran **6a** was not obtained but rearranged product **7a** was formed in low yield. In the presence of only TFAA, successive reactions involving acylation of oxime ether **5**, [3,3]-sigmatropic rearrangement of enehydroxylamine **8**, and intramolecular cyclization of **7** catalysed by TFA proceeded very smoothly. This result contrasts sharply with that in the case of the rearrangement of *N*-trifluoroacetyl enehydrazine **2a** which required higher reaction temperature (above 60 °C) for the successful rearrangement and cyclization.

In order to survey the scope and limitations of the present method, we next investigated the substituent effect on an enamine part (Scheme 3, Table 2). The reaction of **10a** having a



Scheme 3

cyclohexenyl group with TFAA gave dihydrobenzofuran **11a** in 94% yield while the treatment of **10a** with trifluoroacetyl triflate and triethylamine[5] gave the benzofuran **12a** in 85% yield with no isolation of dihydrobenzofuran **11a** (entries 1 and 2). A similar trend was observed in the reaction of acyclic substrates **10b** and **10c** (entries 3–6). Treatment of acyclic substrate **10d** having the phenyl group with trifluoroacetyl triflate gave benzofuran **12d**[6] in 83% yield while the acylation of **10d** with TFAA did not give **11d** and the substrate **10d** was recovered. The structure of cyclized products of either dihydrobenzofuran **11** or benzofuran **12** is dependent on the reaction conditions involving both an acylating agent and base.

Next, we examined a more practical method for performing the preparation and purification of benzofuran simultaneously in a glass tube for column chromatography. The Celite containing TFAA was added to the top of silica gel column. Then, a solution of oxime ether **5** in CH_2Cl_2 was placed on the Celite. After being left for 10 min which is sufficient for the reaction, the mixture was eluted with *n*-hexane–AcOEt (10 : 1) to give dihydrobenzofuran **6a** in 99% yield. This method is very simple and useful for the practical synthesis of dihydrobenzofuran.

We have now established a novel synthetic route to dihydrobenzofurans and benzofurans under the acylating conditions of oxime ether which cause smoothly [3,3]-sigmatropic rearrangement and subsequent cyclization at below room temperature. The new methodology provides a synthetic approach to a wide range of natural products having a benzofuran nucleus.

Representative general procedure

(Table 1, entry 3) To a solution of oxime ether **5** (175 mg, 1 mmol) in CH_2Cl_2 (10 ml) was added TFAA (0.14 ml, 1 mmol) at 0 °C under nitrogen atmosphere. After being stirred at 0 °C for 3 h, the solvent was evaporated under reduced pressure. Purification of the residue by medium-pressure column chromatography (*n*-hexane–AcOEt 5 : 1) afforded dihydrobenzofuran. **6a** (268 mg, 99%) as a pale yellow oil; ν_{max}/cm^{-1} 3422 (NH), 1726 ($NHCOCF_3$); δ_H (500 MHz; $CDCl_3$) 1.59 (1H, m, 2-H), 1.85 (2H, m, 1-H, and 2-H), 2.32 (3H, m, 1-H, and $3\text{-}H_2$), 4.00 (1H, br d, *J* 8.5, 8b-H), 6.78 (1H, br d, *J* 8, 5-H), 6.89 (1H, br s, NH), 6.94 (1H, br t, *J* 8, 7-H), 7.15 (1H, br d, *J* 8, 8-H), 7.16 (1H, br t, *J* 8, 6-H); HRMS (EI) [M^+] calcd for $C_{13}H_{12}F_3NO_2$: 217.0819, found: 217.0820.

NOE was observed between 8b-H (δ 4.00) and NH (δ 6.89) in NOESY spectroscopy.

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