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Boron Trifluoride-assisted Reactions of 1-Benzothiophen-3(2*H*)-one with Various Ketones: a Convenient Entry to 2-Methylene-1-benzothiophen-3(2*H*)-one and/or 6*H*-Di[1]benzothieno[3,2-*b*:2,3-*e*]pyran Derivatives

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The title compounds are obtained in moderate to high yields by BF_3-assisted reaction of 1-benzothiophen-3(2*H*)-one with nine ketones in diethyl ether at room temperature; the relative amounts of pyran **1** and ylidene **2** prove to be dependent upon electronic and steric factors.

The potential hydroxythiophene 1-benzothiophen-3(2*H*)-one (**BT3ONE**).[2] bearing activated hydrogens on the balanced α-methylene component, may attach itself to carbonyl carbons. These aldol type reactions have been shown to be efficient with aryl aldehydes, whereby the formation of 2-[(*Z*)-arylmethylidene]-1-benzothiophen-3-one derivatives occurs with high diastereoselectivity.[3] The addition of non-stabilized carbanions to carbonyl carbons performed with an acid catalyst is one of the most widely employed C–C bond forming reactions in organic synthesis. However, comprehensive updated analysis of the literature reveals that reactions between two different ketones are virtually lacking.[8] One exception would be the heated reaction of **BT3ONE** and acetone in mineral acid to form 6,6-dimethyl-6*H*-di[1]benzothieno[3,2-*b*:2,3-*e*]pyran as the final product.[9] The peculiar heterocyclic ketone **BT3ONE** and its derivatives are a well known class of useful substrates for the production of dyes, photochromic and conductive materials while the pharmaceutical properties of certain derivatives have long been recognised.[1a] In this work, we set up BF_3-assisted reactions of the **BT3ONE** and nine ketones **a**–**i** (*i.e.* acetone, cyclopentanone, cyclohexanone, butan-2-one, ethyl acetoacetate, acetyl trimethylsilane, benzoyl trimethylsilane, 1,1,1-trifluoroacetone and acetophenone) as a possible entry for the transformation of the heterocyclic ring into key substrates for novel materials. For this purpose we carried out a series of standard reactions, arranged in order to obtain best results, using **BT3ONE** and the ketone (**a**–**i**) in dry diethyl ether solutions at room temperature and in the presence of $BF_3{\cdot}OEt_2$. Results are collected in Table 1.

As can be seen from Table 1 the reactivity results are largely dependent on the ketone used with reaction times varying from 15 min to 96 h. Moreover, the procedure allows for efficient access to useful classes of compounds **1** and/or **2**, which are obtained in moderate to high yield. A little 3-hydroxy-2,3′-bibenzothiophene **3**, arising by **BT3ONE** self-condensation was found in the slower reactions. All the compound structures were confirmed by IR, ^1H and ^{13}C-NMR, MS and high resolution MS.

Experimental and theoretical data, performed at the RHF/6-31G* level[16] suggest that the carbonyl oxygen-BF_3 affinity affects the reaction rate to a major extent, while the chemical outcome of the process appears to be dependent on both steric and electronic factors. In rationalising the experimental results one assumes that in the ethereal solution an interaction occurs between the mesomeric **BT3ONE A** with the carbonyl carbon of the ketone–BF_3 complex to generate carbonyl β-OBF_2 intermediate **B** (Scheme 1).

The involvement of intermediate **B** would accord with the fact that standard conditions require at least 1 equiv. of $BF_3{\cdot}OEt_2$ and is consistent with the tetrahedral mechanism that has been previously suggested for reactions involving carbonyl complexes.[16b] This intermediate undergoes loss of $HOBF_2$ to give ylidene **2** (pathway **a**) or undergoes nucleophilic substitution by another **BT3ONE** molecule (pathway **b**). In the latter case, subsequent dehydration of the resulting 1,5-ketoenol bis-adduct **C** finally generates pyran **1** (pathway **b**).

The formal dehydration of **B** to ylidene **2** is expected to be favoured in aldol reactions performed with an acid catalyst. However, in certain cases (*e.g.* entries 1, 3, 4 and 5 in Table 1) pathway **b** to pyran **1** is largely preferred.

Table 1 Reaction times and product distributions[a] for $BF_3{\cdot}OEt_2$-assisted reactions of **BT3ONE** with ketones **a**–**i**

Entry	Ketone	Time/h[b]	**1**	**2**	**3**
1	Acetone **a**	0.3	**a**(82)	**a**(8)	
2	Cyclopentanone **b**	0.15	**b**(—)	**b**(81)	
3	Cyclohexanone **c**	3	**c**(69)	**c**(14)	
4	Butan-2-one **d**	5	**d**(77)	**d** + **d′**(1 : 1)(13)	(2)
5[e]	Ethyl acetoacetate **e**	12	**e**(76)	**e**(—)	(3)
6	Acetyl trimethylsilane **f**	15	**f**(—)	**f**(77)[c]	(4)
7	Benzoyl trimethylsilane **g**	72	**g**(5)[d]	**g**(76.5)	(8)
8	1,1,1-Trifluoroacetone **h**	96	**h** (traces)	**h**(9 : 1)(30)	(15)
9[e]	Acetophenone **i**	96	**i**(10)	**i**(1 : 1)(70)	(10)

[a] Isolated yields (%) based on starting **BT3ONE** (10 mmol). [b] Approximate reaction time for complete consumption of starting material. [c] Recovered as 2-[(*Z*)-ethylidene]-1-benzothiophen-3(2*H*)-one contaminated by < 5% of **2f**. [d] Recovered as 6-phenyl-6*H*-di[1]benzothieno[3,2-*b*:2,3-*e*]pyran. [e] This reaction was also carried out with 4 equiv of $BF_3{\cdot}OEt_2$ without substantial alteration in the product yields.

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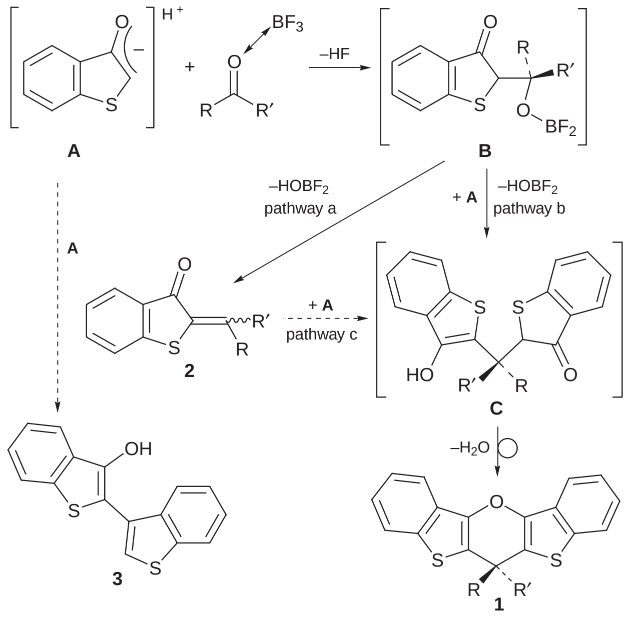

Scheme 1

Some *gem*-dialkyl stabilising effect of the monomolecular mechanism at the level of the incipient α-carbocation, C–OBF$_2$ of **B**, probably plays an important role. Pathway **b** proves to be more favoured in the virtual absence of steric factors. For example, in the cases of larger rings and/or small dialkyl substituted ketones it is apparent that the formation of pyran **1** derivatives is favoured, whereas, as in the case of cyclopentanone, decreasing the ring size brings about enhancement of yields of ylidene **2**. For 1,1,1-trifluoroacetone electronic factors appear to be responsible for the inhibition of formation of pyran **1**, owing to the presence of the electron-withdrawing trifluoromethyl group which destabilizes the possible production of an incipient carbocation.

Experimental

General Procedure for the Reactions of **BT3ONE** *with Ketones* **a**–**i** *in the Presence of* BF$_3$·OEt$_2$.—To dry diethyl ether solutions (20 cm^3) of **BT3ONE** (10 mmol) and 1 equiv (10 mmol) of the appropriate ketone is added by syringe BF$_3$·OEt$_2$ (20 mmol, 2.6 cm^3). The resulting solutions were stirred in a sealed tube at room temperature for the appropriate time, until TLC showed the absence of **BT3ONE**. The residue, obtained after careful neutralisation with saturated sodium hydrogen carbonate water solution and work-up, was chromatographed on a silica column using light petroleum (bp 40–60 °C) with an increasing amount of diethyl ether (up to 80%) as eluent. An aliquot of each reaction mixture was analysed by GC–MS before chromatographic separation.

Techniques used: ^{1}H and ^{13}C NMR, mass spectrometry, GC–MS, *ab initio* calculations

References: 22

Table 2: *Ab initio* theoretical results, total energies, zero-point energies and BF$_3$ affinities

Figures: 2

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