Direct Preparation of Benzofurans from *O*-Arylhydroxylamines

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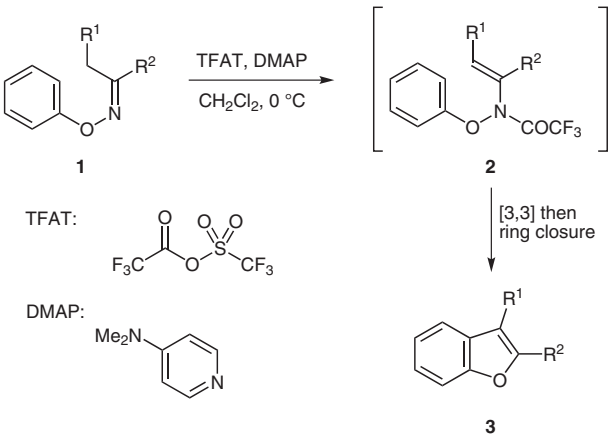
Abstract: Reaction of *O*-arylhydroxylamine hydrochlorides with either cyclic or acyclic ketones in the presence of methanesulfonic acid leads directly to the benzofuran derivative via a proposed one-pot condensation–rearrangement–cyclisation reaction sequence in good to excellent yields.

Key words: benzofuran, hydroxylamine, sigmatropic rearrangement

The benzofuran nucleus represents an important pharmacophore embedded within the structure of a range of natural and synthetic compounds which display a broad range of biological activities.[1] This has rendered benzofurans important synthetic targets.[2] An overview of current methods available for the preparation of benzofurans has recently been reported[3] which reveals the range of innovative disconnection strategies to access this heterocyclic motif. This number of methods highlights the significance of the scaffold as a synthetic target.

Of the methods available to prepare benzofurans one of the most synthetically accessible involves [3,3]-sigmatropic rearrangement of preformed *O*-aryl oxime ethers **1** promoted by Brønsted or Lewis acids.[4] More recently, Naito and co-workers have shown this reaction can also be triggered by N-trifluoroacetylation of the oxime ether **1** with trifluoroacetyl triflate (TFAT) providing access to benzofurans **3** (Scheme 1).[5] Within this report it was shown that treatment of *O*-aryl oxime ether **1** with trifluoroacetic acid did not lead to the benzofuran **3** (at room temperature) and it was concluded that N-acylation was the crucial step for [3,3]-sigmatropic rearrangement.

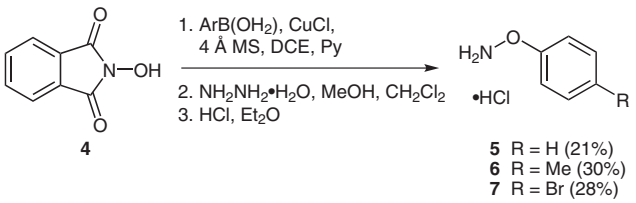
Over recent years we have prepared a variety of hydroxylamine reagents[6] for the α-oxygenation of carbonyl compounds[7] and the functionalisation of aromatic rings[8] via a proposed [3,3]-sigmatropic rearrangement strategy. We were intrigued whether this approach to bond construction was also applicable to C–C bond formation through the use of *O*-arylhydroxylamine reagents such that suitable conditions could be found to directly convert a ketone to the corresponding benzofuran. Success of this strategy would require discovery of acidic reaction conditions that could trigger the rearrangement of intermediate oxime ethers analogous to **1** in a similar manner to the well-established Fischer indole synthesis.[9]



Scheme 1 Reaction of *O*-aryl oxime ethers **1** with TFAT and DMAP

Within this report we show that reaction of *O*-arylhydroxylamine hydrochloride salts **5**–**7** with cyclic or acyclic ketones in the presence of methanesulfonic acid provides a convenient and direct method for the preparation benzofuran derivatives. This allows access to benzofurans under mild reaction conditions without the need for initial oxime formation or trifluoroacetylation of the hydroxylamine nitrogen.

Our investigations began with the preparation of *O*-arylhydroxylamine salts **5**–**7**. Two synthetic routes have recently been reported for the preparation of this class of compound. The first involves the O-arylation of *N*-hydroxyphthalimide **4** followed by deprotection and salt formation.[10] The second involves a copper-catalysed O-arylation of benzaldehyde oxime.[11] In our hands, the Sharpless method proved to be higher yielding and more amenable to scale-up. We therefore adopted this method for the preparation of **5**–**7** which were used within this investigation (Scheme 2). It is noteworthy that this method of O-arylation has been shown to be effective for a variety of different arylboronic acids other than those adopted within the current work; therefore, the methodology described within this communication should be applicable to other *O*-arylhydroxylamine substrates.



Scheme 2 Preparation of *O*-arylhydroxylamine hydrochlorides

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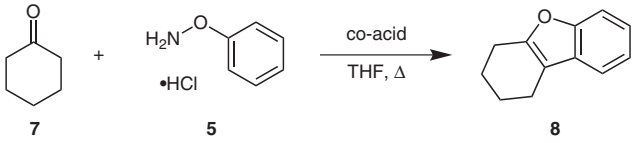
Selected results for the optimisation of reaction conditions are outlined in Table 1. In agreement with previous findings, reaction of *O*-phenylhydroxylamine hydrochloride **5** (1 equiv) with cyclohexanone **7** (1 equiv) at room temperature failed to produce any of the benzofuran (entry 1). Encouragingly, warming the reaction mixture to 60 °C provided some benzofuran (25%; entry 2). Crucial to optimising the desired benzofuran synthesis was the addition of a co-acid. After much experimentation, methanesulfonic acid emerged as the acid of choice (entries 3 and 4). Optimal reaction conditions involved reaction of **5** (1 equiv) with **7** (1 equiv) at 60 °C (oil bath temperature) in THF for two hours, the benzofuran **8** being isolated in a pleasing 70% yield after purification by column chromatography (entry 4).[12]

Table 1 Optimisation of Benzofuran Synthesis[a]

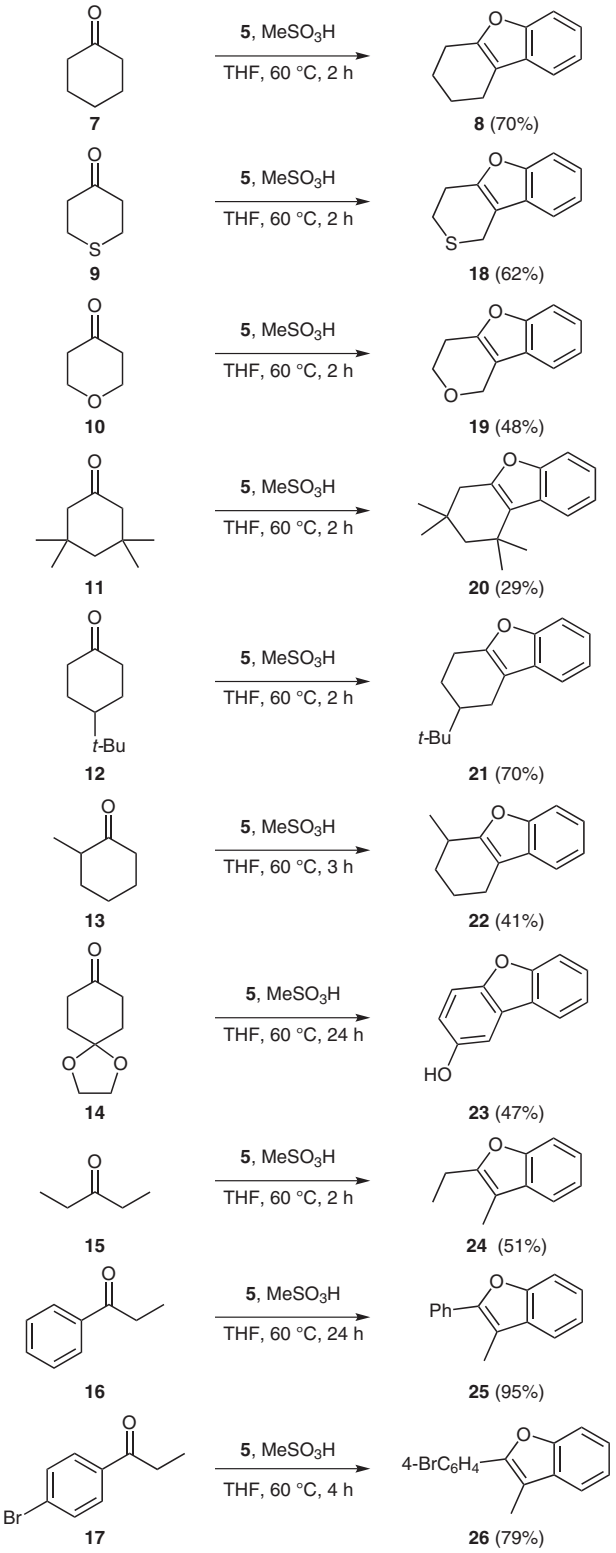


7 **5** **8**

Entry	Co-acid (equiv)	Time (h)	Temp (°C)	Yield (%)[b]
1	none	2	r.t.	–
2	none	2	60	25
3	$MeSO_3H$ (1.5)	1	60	42
4	$MeSO_3H$ (2.0)	2	60	70

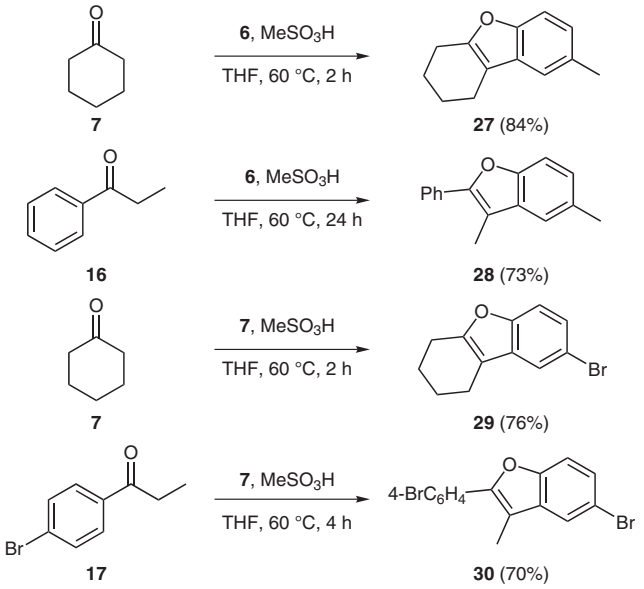
[a] All reactions performed at 0.5 M concentration in THF with 1 equivalent of cyclohexanone **7** and 1 equivalent of *O*-phenylhydroxylamine hydrochloride **5**.
[b] Isolated yield of **8**.

Having found efficient conditions for the transformation a series of alternative cyclic and acyclic ketone substrates were examined to discover some of the scope and limitations of the process (Scheme 3). Use of heteroatom-substituted cyclic ketones **9** and **10** provided simple access to the interesting heterocycles **18** (62%) and **19** (48%) under the standard reaction conditions. In line with the proposed formation of an intermediate imine the reaction appears to be influenced by sterics, with the tetramethyl-substituted cyclohexanone **11** leading to a substantially reduced yield of the benzofuran **20** (29%) under standard conditions, however, the product could easily be isolated analytically pure after chromatography. Moving the steric bulk away from the carbonyl group with 4-*tert*-butylcyclohexanone (**12**) restored the reaction efficiency (**21**; 70%). Use of the nonsymmetrical 2-methylcyclohexanone (**13**) resulted in selective enamine formation at the secondary centre to give benzofuran **22** (41%). The acidic reaction conditions necessary for the transformation will obviously restrict functional group tolerance of the overall transformation. Interestingly, reaction of the ketal containing substrate **14** allowed formation of the nonsymmetrical dibenzofuran **23** (47%) when reacted for an extended period of time (24 h). Along with the cyclic ketones discussed above, aliphatic and aromatic acyclic substrates **15**–**17** were also effective within the transformation giving the benzofurans **24**–**26** in good to excellent yield (51–95%). Although far from an exhaustive list of possible carbonyl substrates, the standard reaction conditions adopted in the majority of these transformations [60 °C, 2 h, THF, $MeSO_3H$ (2 equiv)] suggest that specific optimisation will provide an efficient and direct means to access a diverse array of benzofuran products.



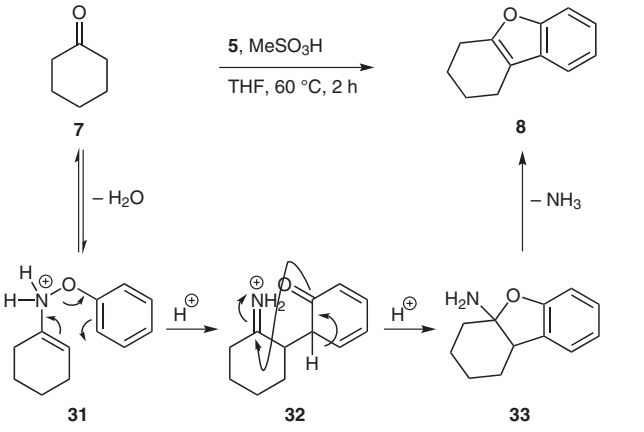
Scheme 3 Alternative ketone substrates **9**–**17**

Examination of the alternative hydroxylamine salts **6** and **7** showed a similar reactivity profile with both cyclic and acyclic ketones allowing access to the corresponding benzofuran derivatives **27**–**30** (70–84%; Scheme 4).



Scheme 4 Alternative hydroxylamine salts **6** and **7**

A plausible mechanistic pathway for the transformation is outlined in Scheme 5. Condensation of the salt **5** with cyclohexanone (**7**) should lead to the protonated enamine **31** which can then undergo a [3,3]-sigmatropic rearrangement under the acidic reaction conditions. Rearomatisation and intramolecular cyclisation followed by elimination of ammonia would then provide the observed product **8**.



Scheme 5 Proposed mechanistic pathway

In conclusion, we have described a simple method for the direct formation of benzofurans from *O*-arylhydroxylamine hydrochlorides and cyclic or acyclic ketones. The reaction proceeds without the need for purification of solvents or the exclusion of moisture and air, greatly adding to the practicality of the method. Specific advantages over existing literature methods include the fact that isolation of the intermediate *O*-aryl oxime ether is not necessary and by heating the reaction system in the presence of a suitable co-acid reagents such as trifluoroacetyl triflate and 4-(*N*,*N*-dimethylamino)pyridine can be avoided.

Acknowledgement

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(12) **Typical Experimental Procedure**; **1,2,3,4-Tetrahydrodibenzofuran (8)**:[13] *O*-Phenylhydroxylamine hydrochloride (0.146 g, 1 mmol) was dissolved in THF (2 mL) and warmed to 60 °C. After 5 min methanesulfonic acid (0.150 g, 2 mmol) and cyclohexanone (0.100 g, 1 mmol) were added and the reaction was monitored by TLC. On completion, the solvent was removed under reduced pressure. Purification by column chromatography (PE–EtOAc, 20:1) gave the title compound **8** (0.121 g, 70%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.32 (m, 2 H), 7.06–7.12 (m, 2 H), 2.62–2.66 (m, 2 H), 2.50–2.54 (m, 2 H), 1.80–1.86 (m, 2 H), 1.71–1.78 (m, 2 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 154.4, 154.0, 128.9, 123.0, 122.1, 118.4, 112.9, 110.8, 23.5, 23.0, 22.7, 20.5. LRMS (EI^+): *m*/*z* = 172.1 $[M]^+$. HRMS (MALDI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{12}O$: 172.0883; found: 172.0880.

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