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Preparation of Highly Functionalised Benzofurans from *ortho*-Hydroxyphenones and Dichloroethylene: Applications and Mechanistic Investigations

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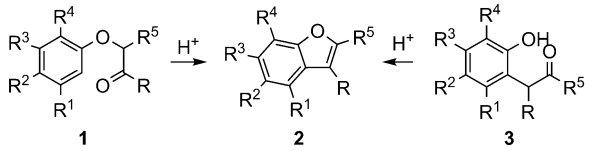
Abstract: Highly functionalised benzofurans have been prepared from *ortho*-hydroxyphenones and 1,1-dichloroethylene. The key intermediate, a chloromethylene furan, smoothly rearranged into the corresponding benzofuran carbaldehyde under acidic conditions. Some mechanistic investigations have been performed and several biologically active benzofurans have been synthesised.

Keywords: acid catalysis · benzofurans · heterocycles · NMR spectroscopy · rearrangement

Introduction

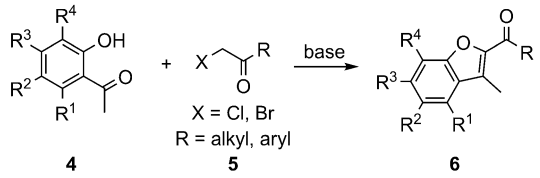
Benzofurans are important heterocyclic compounds. Their widespread occurrence and powerful biological activities have stimulated the development of numerous synthetic methods. These approaches can be divided into four main strategies. The dehydration–cyclisation of *o*-hydroxybenzyl ketones **3** or α-(phenoxy)alkyl ketones[1–3] **1** are two well-known methods (Scheme 1), described among others, by Boehme and Adams.



Scheme 1. Dehydration–cyclisation pathways.

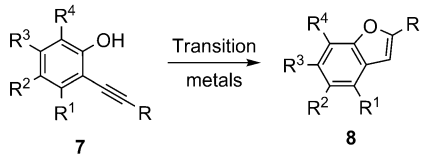
The one-pot etherification and dehydration–cyclisation of *o*-hydroxyacetophenones **4** under basic conditions[3–6] is another general approach that has been described, for example, by Bogdal and Katrizky (Scheme 2).

Finally, a last approach consists of the cyclisation of arylacetylenes using transition-metal catalysts[7–13] as described by



Scheme 2. One-pot etherification and dehydration–cyclisation.

Patel, Cacchi and many others (Scheme 3). At this stage, it is important to point out that several alternative, though less general, methodologies[14–24] have also been described. These involve ring fragmentations[25–27] and oxidative processes.[28–30]



Scheme 3. Arylacetylene cyclisation using transition metals.

Recently, we reported some preliminary results on a novel benzofuran synthesis,[31] based upon our previous incursion into the largely unexplored *Z*-chloromethylene ketal chemistry.[32] Thus, starting from a variety of *o*-hydroxyphenones **9** and 1,1-dichloroethylene, a range of chloromethylene furans **10** could be obtained in high yield. These labile intermediates were then rearranged under acidic conditions, yielding benzofurans **11** in excellent overall yields (Scheme 4).

Herein, we disclose our results in full and discuss the scope and limitations of our method, with respect to both reaction partners. In addition, some of the mechanistic information gathered during our studies will be presented.

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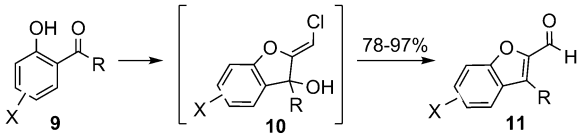
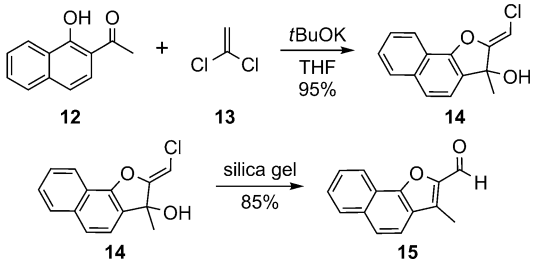


Scheme 4. Transformation of *o*-hydroxyphenones into benzofuran carbaldehydes.

Results and Discussion

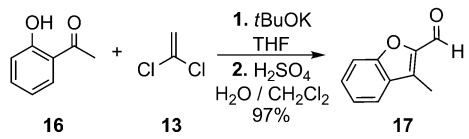
The rearrangement: When an α-hydroxyphenone is treated with 1,1-dichloroethylene and a base, such as *t*BuOK, a rapid reaction ensues and leads to a chloromethylene furan. Our previous study demonstrated that potassium *tert*-butoxide deprotonated dichloroethylene **13**, which led to the in situ generation of the corresponding chloroacetylene anion.[33,34] This intermediate then adds to the ketone, for example, 2-acetylnaphth-1-ol (**12**; Scheme 5). At this stage, a spontaneous 5-*exo*-*dig* ring closure of the alkoxide occurs, leading to the formation of the chloromethylene furan **14** in 95% estimated yield. Much to our surprise, only aldehyde **15** was isolated after purification by chromatography on silica gel.



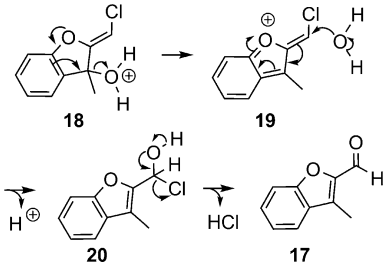
Scheme 5. Formation of the naphthylfuran carbaldehyde.

The same conditions were applied to *o*-hydroxyacetophenone (**16**; Scheme 6). This time, the rearrangement did not occur spontaneously on silica gel. Therefore, a biphasic acidic hydrolysis protocol was developed. Under these conditions, aldehyde **17** could then be obtained in 97% yield.

These results suggest that, under acidic conditions, oxonium cation **19** is formed by water elimination from **18** (Scheme 7). Water then adds back at the terminal position of **19**, which leads to α-chlorohydroxybenzofuran (**20**), which spontaneously eliminates HCl, generating aldehyde **17**.

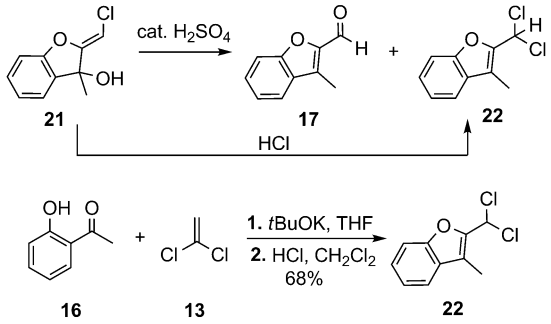


Scheme 6. Formation of the methylbenzofuran carbaldehyde.



Scheme 7. Proposed mechanism for the rearrangement step.

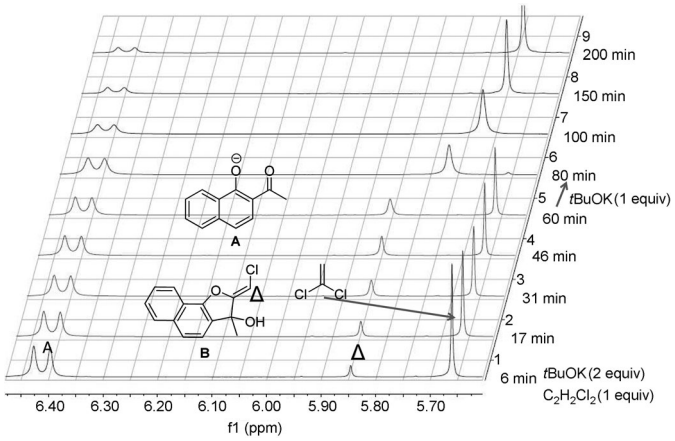
Several acids were screened under homogeneous and heterogeneous conditions. Sulfuric acid in CH_2Cl_2/H_2O eventually provided optimum conditions. When the rearrangement was carried out in a homogeneous medium, or neat and without acid, a 1:1 mixture of the aldehyde **17** and of the dichlorinated product **22** was consistently obtained. When hydrochloric acid was used, adduct **22** could be isolated as the major product (Scheme 8).



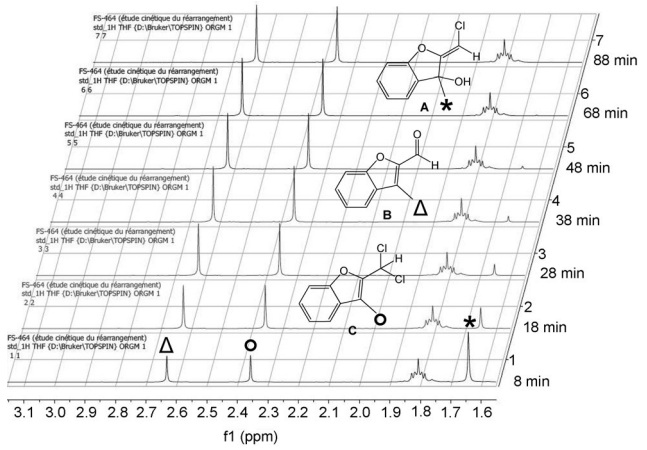
Scheme 8. Preparation of the dichlorinated adduct.

According to our mechanistic hypothesis, HCl is released during the rearrangement. This acid can then competitively react with the chloromethylene ketal, thereby leading to the dichlorinated adduct **22**. Our hypothesis also explains the observed 1:1 ratio of **17** and **22**. Indeed, if one molecule of water adds to the exomethylene position of oxonium **19**, a chloride ion is produced. In a homogeneous medium, this ion will be rapidly consumed by its addition onto a second oxonium cation, which provides the dichlorinated product **22**. Therefore, a biphasic system containing dichloromethane and water was used. It proved to be quite successful. Indeed, in this system, the hydrochloric acid is rapidly hydrated by water, thus minimising the re-addition of the chloride ion. Moreover, aldehyde **17** is extracted in the organic layer as soon as it is generated.

Mechanistic investigations: To lend some more support to our mechanistic proposal, the formation of chloromethylene furan **21** was followed by ^{1}H NMR spectroscopy in deuterated THF (Scheme 9). As expected, no aldehyde could be detected during this step, thereby confirming that the rearrangement occurred during the acidic treatment. Moreover,



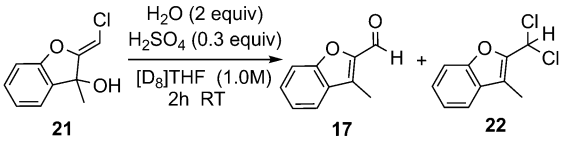
Scheme 9. Chloromethylene furan formation followed by ^{1}H NMR spectroscopy.



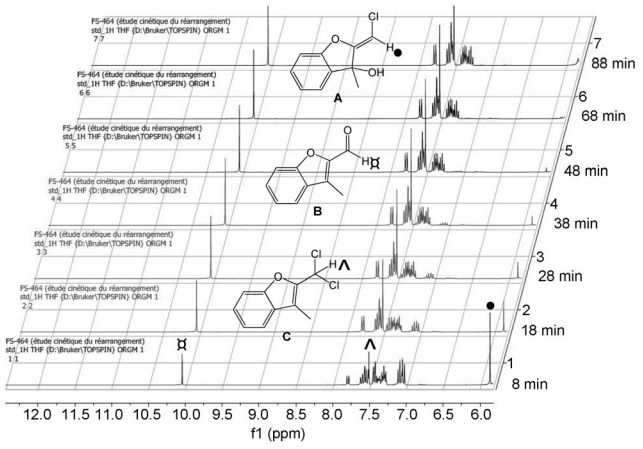
Scheme 12. NMR spectroscopy experiment for the rearrangement step (aliphatic area).

it can be seen that the chloromethylene proton appeared slowly after the disappearance of the dichloroethylene protons, which reinforces our previously postulated mechanism.[31]

The rearrangement of the chloromethylene furan **21** was studied in a similar way (Scheme 10). The reaction was performed in THF, at a concentration of 1.0 M, at room temperature. Water (2 equiv) and sulfuric acid (0.3 equiv) were then added and the transformation was monitored. These conditions are known to produce adducts **17** and **22** in a 1:1 ratio. The spectra are displayed in Schemes 11 and 12. In the aromatic region, the characteristic protons of aldehyde **17** ($\delta = 10.04$ ppm), dichlorinated adduct **22** ($\delta = 7.50$ ppm) and chloromethylene reactant **21** ($\delta = 5.86$ ppm) are indicated (Scheme 11). A similar analysis was performed for the aliphatic region. The methyl protons of **17** ($\delta = 2.63$ ppm), **22** ($\delta = 2.35$ ppm) and **21** ($\delta = 1.64$ ppm) were assigned (Scheme 12). As expected, the signals of **17** and **22** appeared in a 1:1 ratio, proportionally to the disappearance of the chloromethylene signals.

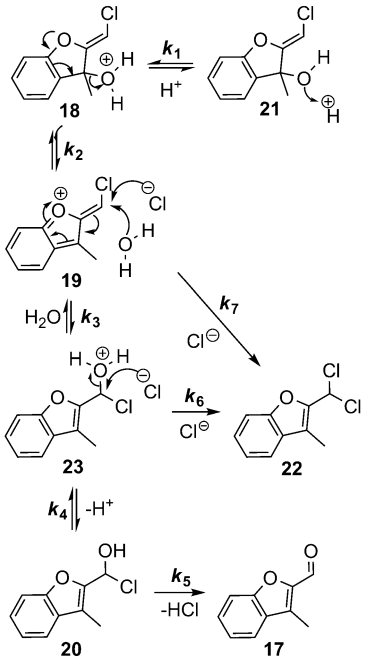


Scheme 10. Conditions for the NMR spectroscopy investigations of the rearrangement step.



Scheme 11. NMR spectroscopy experiment for the rearrangement step (aromatic area).

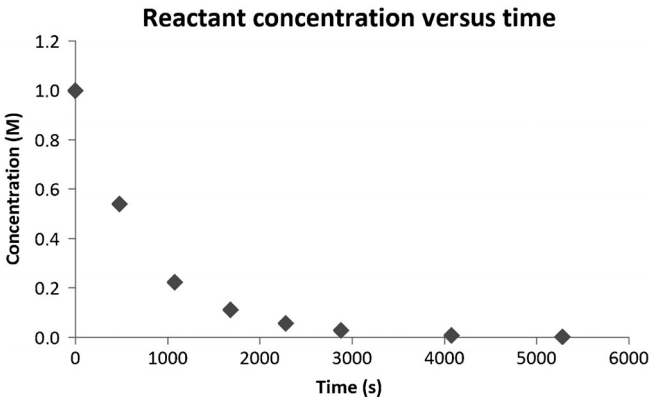
The mechanistic pathway can be considered as shown in Scheme 13. The chloromethylene furan **21** is protonated reversibly (k_1), leading to hydronium cation **18**. An oxonium ion **19** is then formed (k_2) by elimination of water. Addition of water to this oxonium cation (k_3) leads to the intermediate **23**. A chloride anion can also competitively react with



Scheme 13. Detailed mechanistic pathway for the rearrangement step.

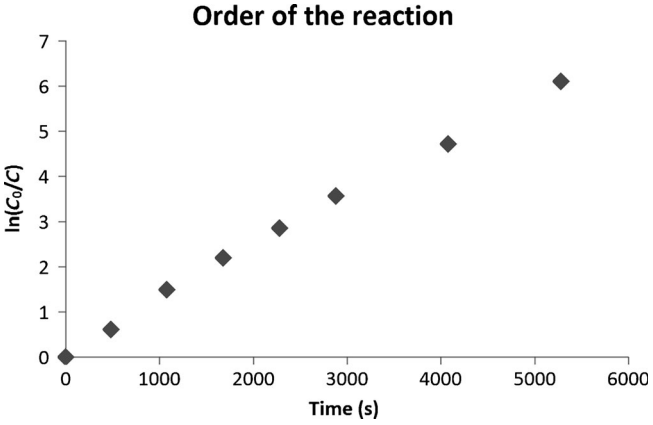
this molecule (k_6) or add to the oxonium species **19** (k_7) to form the dichlorinated product **22**. Intermediate **23** may lose a proton (k_4), yielding the α-chloroalcohol **20**. Finally, aldehyde **17** would be obtained after loss of HCl (k_5).

The NMR spectroscopy data also enabled us to obtain some kinetic values for this mechanistic scheme. As an initial hypothesis, we suspected the oxonium cation formation (k_2) to be the rate-determining step of the whole process. Therefore, the disappearance of the starting material was followed by ^{1}H NMR spectroscopy, using the methyl signal located at $\delta = 1.64$ ppm. The obtained exponential curve is depicted in Scheme 14.



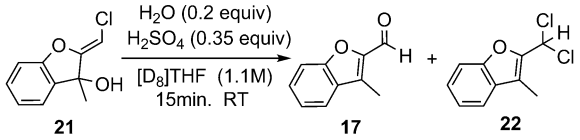
Scheme 14. Concentration of the chloromethylene furan versus the reaction time.

Interestingly, a first-order correlation was obtained by plotting the logarithm of the concentration ratio ($\ln(C_0/C)$ versus the reaction time (Scheme 15). As aldehyde **17** and chlorinated product **22** are always formed in a 1:1 ratio, even after 8 min, k_4, k_5, k_6 and k_7 are high compared to the rate-determining step, and all the HCl is immediately consumed. Therefore, H_2SO_4 becomes rapidly the catalytically active acid and its concentration remains essentially constant. With this information, the first-order kinetics match the oxonium cation formation perfectly.



Scheme 15. Linear regression ($\ln(C/C_0)$) for the chloromethylene furan rearrangement.

Another NMR spectroscopy study was performed to investigate the effect of water. As mentioned earlier, performing the reaction in THF, at a concentration of 1.1 M, at room temperature, in the presence of water (0.2 equiv) and sulfuric acid (0.35 equiv), led to the formation of adducts **17** and **22** in a 1:1 ratio (Scheme 16).

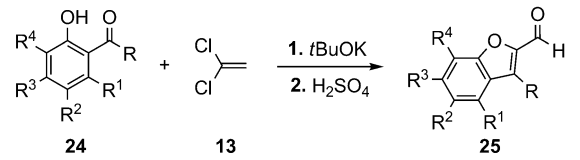


Scheme 16. Increasing the amount of water in the rearrangement step.

Surprisingly, the reaction reached completion within 15 min but a confident kinetic correlation could not be obtained. However, this experiment indicates that the addition of water to the oxonium cation (k_3) could not be the rate-determining step. Indeed, when the amount of water is lowered, the reaction proceeds faster. This effect could be due to the hydration and dilution of the HCl, lowering the effective concentration in acid and thus decreasing the reaction rate.

In conclusion, our NMR spectroscopy studies enabled us to observe the formation of the chloromethylene furan intermediate. We have also established a first-order kinetic profile, strongly suggesting the generation of the oxonium cation **19** to be the rate-determining step.

Preparation of benzofurans: Using our two-step procedure, several commercially available *o*-hydroxyphenones **24** were successfully transformed into the corresponding benzofurans **25** in 78 to 97% isolated yield (Scheme 17).

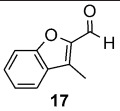
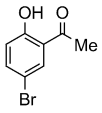
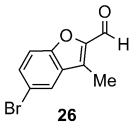
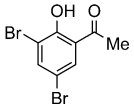
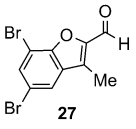
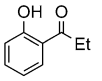
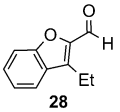
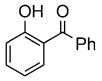
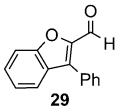
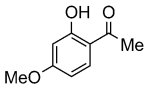
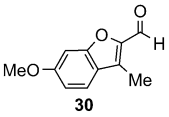
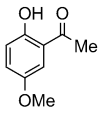
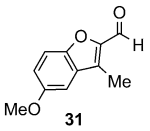
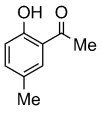
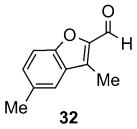
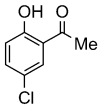
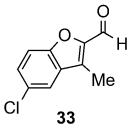
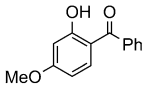
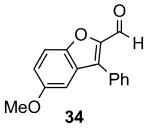
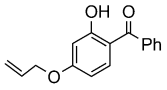
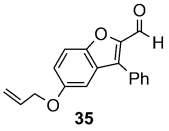


Scheme 17. Extension of our methodology to several hydroxyphenones.

The reaction appears to be rather general and is efficient for both alkyl- and aryl-substituted phenones (Table 1). It also tolerates several functions such as halides and alkoxy groups. We noticed a significant effect of the substituents on the kinetics of the rearrangement. Indeed, for electron-withdrawing groups, the reaction is slow. In contrast, when electron-donating substituents are present, this step is rather fast. These observations are in agreement with the formation of an oxonium cation as the rate-determining step.

To extend our method to the corresponding aldehydes, we had to modify slightly our system, as a fast degradation occurred using the standard procedure. Thus, lithium diisopropylamide (LDA) was used to prepare the chloroacetylene

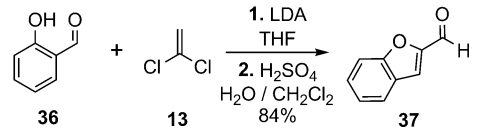
Table 1. Preparation of benzofuran carbaldehydes.

Entry	Substrate	Product	Yield[a] [%]
1		 **17**	97
2		 **26**	93
3		 **27**	78
4		 **28**	92
5		 **29**	94
6		 **30**	88
7		 **31**	93
8		 **32**	80
9		 **33**	89
10		 **34**	94
11		 **35**	95

[a] All yields are for pure, isolated products.

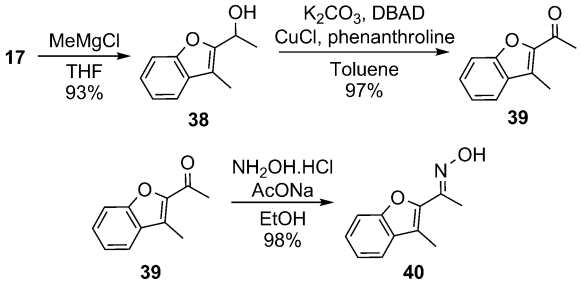
anion and salicylaldehyde **36** was added dropwise to the solution containing this lithiated anion. After an acid-catalysed rearrangement, benzofuran-2-carbaldehyde **37** was isolated in 84% yield (Scheme 18).

Using our methodology, nerolione **39** was readily assembled as shown in Scheme 19. However, our spectroscopic data did not match those reported in the literature.[35] Therefore, to establish unambiguously the structure of our compound, the corresponding oxime **40** was prepared and crystallised. A single-crystal X-ray diffraction analysis confirmed our assignment (Scheme 20); the previous data in the literature are thus incorrect.



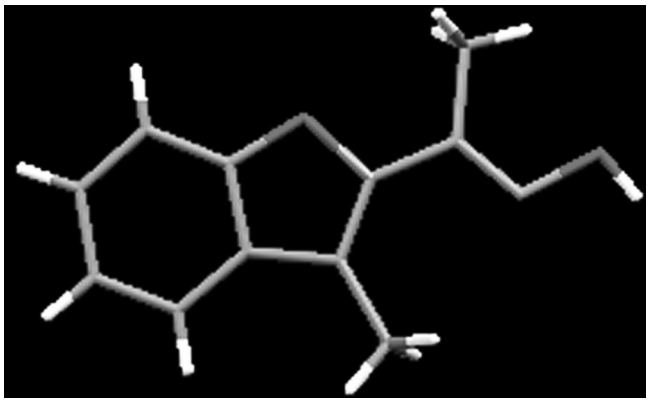
36 **13** **37**

Scheme 18. Formation of the benzofuran-2-carbaldehyde with LDA.



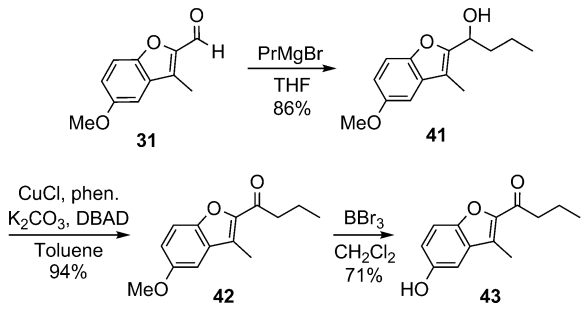
17 **38** **39** **39** **40**

Scheme 19. Synthesis of nerolione.



Scheme 20. X-ray plot of nerolione oxime **40**.

Starting from the benzofuran aldehyde **31**, the lipoxygenase inhibitor **43** was also prepared (Scheme 21). Alcohol **41** was obtained in good yield by the addition of the propyl Grignard reagent. It was then oxidised using our copper-cat-

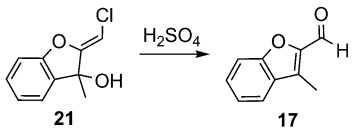


31 **41** **42** **43**

Scheme 21. Synthesis of a lipoxygenase inhibitor.

alysed method.[36] Finally, demethylation of ketone **42** proceeded smoothly, using a standard protocol,[37] delivering the desired compound in high overall yields.

Aware that the conditions used to rearrange the chloromethylene furans require a prolonged period of time, we varied the acid concentration and the reaction temperature to speed up the process. Chloromethylene furan **21** was chosen as a model substrate and was transformed into the benzofuran aldehyde **17** (Scheme 22).



Scheme 22. Optimisation of the rearrangement step.

As can be seen from the Table 2, increasing the concentration of H_2SO_4 results in a significant decrease in the reaction time, without deleterious effects on the yield of the final adduct. In a similar manner, raising the temperature to 83 °C and using dichloroethane instead of dichloromethane led to a reasonable increase in the reaction rate. These conditions were then selected as the optimum ones and used in all subsequent experiments.

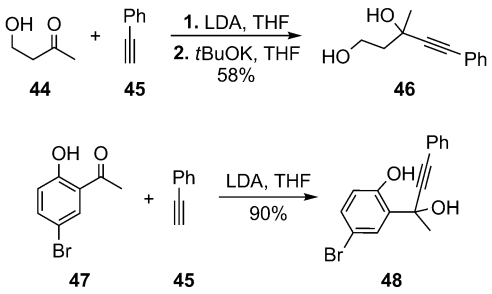
Table 2. Conditions for the rearrangement of the chloromethylene furan **21**.

$H_2SO_{4(aq)}$ [M]	Solvent	T [°C]	t [h]	Yield [%]
0.01	CH_2Cl_2	20	24	98
0.1	CH_2Cl_2	20	10	93
1.0	CH_2Cl_2	20	6	97
0.01	CH_2Cl_2	40	8	97
0.01	DCE	83	<1	98
0.01	toluene	110	<1	93

[a] DCE = 1,2-dichloroethane.

Acetylene chemistry: As chloroacetylene proved to be an efficient partner in our transformation, we wondered whether other substituted acetylenes could also be used in this benzofuran synthesis.

At the onset of our study, phenylacetylene was treated with 4-hydroxy-2-butanone (**44**) and 5-bromo-2-hydroxyacetophone (**47**; Scheme 23). Although potassium *tert*-butoxide

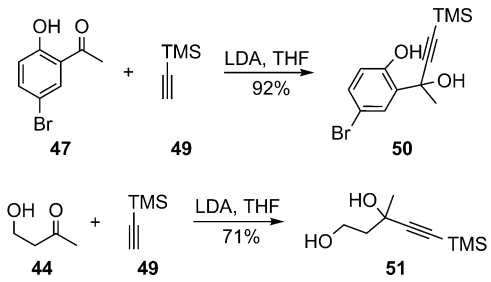


Scheme 23. Reaction of phenylacetylene with model substrates.

could not deprotonate this acetylene, treatment with LDA afforded the corresponding diols **46** and **48**. Both diols were then reacted with *t*BuOK. Alas, no ring closure was observed.

To verify that an alternative mechanism does not occur when a haloalkene is used as the alkyne precursor, β-bromostyrene (2.2 equiv) was reacted with an excess amount of LDA (4.4 equiv) in the presence of ketone **47**. As expected, and in perfect agreement with our proposed mechanism, adduct **48** was obtained in essentially quantitative yields, hence ruling out a possible cyclisation pathway not involving the intramolecular addition of the alkoxide anion on the in situ generated alkyne intermediate.

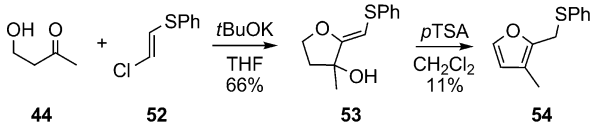
A similar lack of reactivity was noticed in the case of trimethylsilyl (TMS)-acetylene (**49**; Scheme 24) and LDA had to be used to remove the acetylenic proton. Diols **50** and **51** were obtained from the corresponding ketones **47** and **44**.



Scheme 24. Reaction of trimethylsilylacetylene with model substrates.

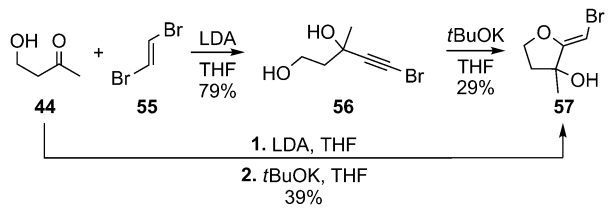
Treatment of diol **50** with *t*BuOK led to the recovery of the starting material. Under the same conditions, loss of the TMS group was observed in the case of diol **51**. It thus transpires that the TMS substituent, as the phenyl group, is unable to stabilise the formal negative charge generated at its α position during the 5-*exo*-*dig* ring closure.

When **44** was treated with the thiophenylacetylene precursor **52**,[38] in the presence of *t*BuOK, the corresponding *exo*-methylene furan **53** was obtained in 66% yield (Scheme 25).



Scheme 25. From 4-hydroxy-2-butanone to a thiophenyl-substituted furan.

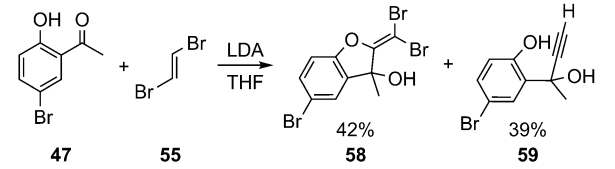
To our surprise, this intermediate was found to aromatise under acidic conditions, albeit in a modest yield. A similar sequence was attempted with **47** but no reaction occurred. It thus transpires that the thiophenyl acetylene anion is not reactive enough to add to the less electrophilic 5-bromo-2-hydroxyacetophenone. In the presence of other bases, such as LDA, degradation of the thiophenylacetylene precursor was observed and the desired product was not obtained.



Scheme 26. Reaction of 4-hydroxy-2-butanone with dibromoethylene.

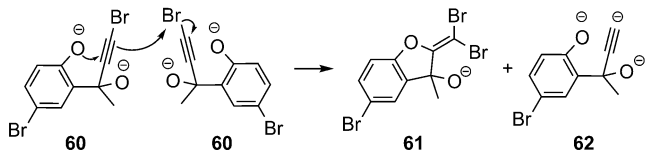
As 1,1-dichloroethylene provides chloroacetylene,[33,34] we wondered whether 1,2-dibromoethylene (**55**) could be a precursor for bromoacetylene (Scheme 26). Unfortunately, rapid decomposition was observed in the presence of *t*BuOK. Formation of bromoacetylene could, however, be accomplished with LDA. The subsequent addition of 4-hydroxy-2-butanone (**44**) provided the desired diol **56** in excellent yield. Treatment of **56** with *t*BuOK, at −24 °C, to promote the 5-*exo*-*dig* cyclisation, resulted in the formation of bromomethylene furan **57** in a modest yield. A sequential process in which intermediate adduct **56** was not purified but directly treated with *t*BuOK resulted in an improved yield of 39 %.

When aromatic ketone **47** was treated under the same conditions, a rather unexpected transformation occurred (Scheme 27) and two products could be identified. The first one proved to be the dibromomethylene benzofuran **58** and the second one the non-brominated acetylenic diol **59**.



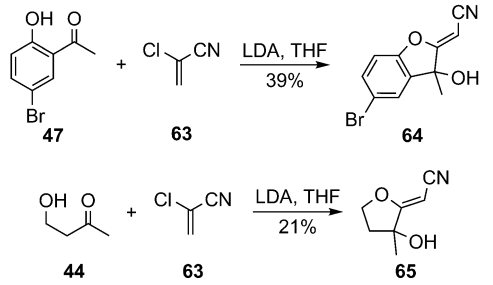
Scheme 27. Reaction of 5-bromo-2-hydroxyacetophenone with dibromoethylene.

This result can be rationalised as follows: during the ring closure of bromoacetylene intermediate **60**, the bromine atom of **60** is transferred to the growing partial negative charge generated on a second molecule of **60**. This negative-charge buildup results from the intramolecular addition of the phenoxide anion onto the triple bond (Scheme 28). This reaction should provide anions **61** and **62** in a 1:1 ratio. Protonation during the workup ultimately afforded the final adducts **58** and **59**.



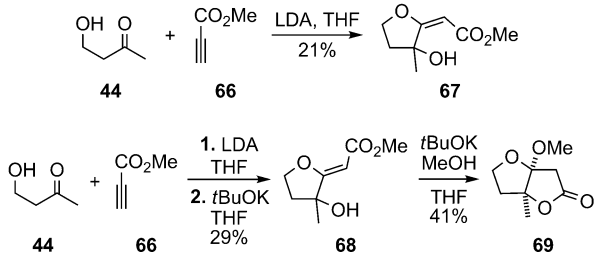
Scheme 28. Bromine-exchange reaction.

The use of 2-chloroacrylonitrile (**63**) as a precursor of cyanoacetylene proved to be successful and cyanomethylenes **64** and **65** could be isolated in moderate yields (Scheme 29). Extensive polymerisation was observed and further attempts to optimise this reaction failed.



Scheme 29. Reaction of 2-chloroacrylonitrile with model substrates.

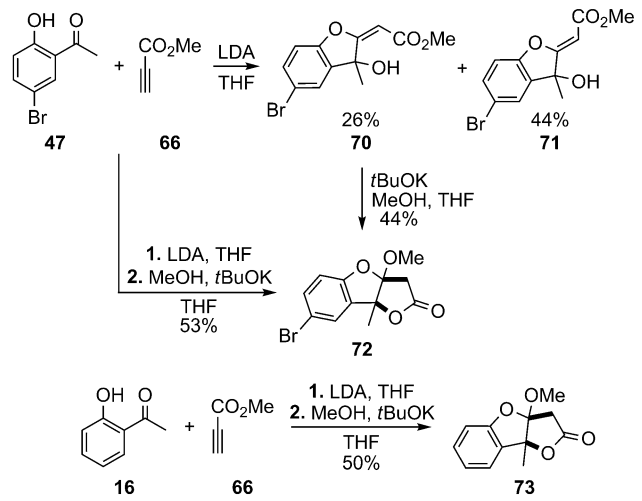
Using an alkyne substituted by an ester group proved to be even more interesting. When methyl propiolate **66** was reacted with *t*BuOK, polymerisation occurred. However, using LDA, the corresponding *exo*-methylene ester **67**, derived from 4-hydroxy-2-butanone **44**, could be obtained in a modest yield (Scheme 30). However, and for the first time,



Scheme 30. Reaction of 4-hydroxy-2-butanone with methyl propiolate.

the double-bond geometry was determined as *E*, a dramatic deviation from all the previous examples. It is possible that the ring closure, in this case, proceeded through an allenyl enolate, which was subsequently protonated. In contrast, sequential treatment (LDA, workup, then *t*BuOK) of **44** led to the *Z*-methylene ester **68**. Both unsaturated esters **67** and **68** underwent the Michael addition of methanol, followed by a spontaneous lactonisation, to afford the interesting adduct **69**.

In the aromatic series, the coupling between 5-bromo-2-hydroxyacetophenone **47** and methyl propiolate afforded the two methylene ester isomers **70** and **71** in a combined 70 % yield (Scheme 31). Lactone formation was also observed when **72** was treated with methanol (1.5 equiv) and *t*BuOK (1.8 equiv). Further optimisation, using a sequential process, provided the tricyclic lactone **72** in 53 % overall yield from **47**. This transformation was extended to 2-hydroxyacetophenone **16**. The corresponding lactone **73** was obtained in 50 % yield.



Scheme 31. Reaction of acetophenones with methyl propiolate.

The successful addition/cyclisation sequence described above depends critically upon the nature of the electron-withdrawing group attached to the in situ generated alkyne. This reactivity correlates particularly well with the Hammett σ_I coefficients, also known as the induction sigma coefficients or electron-withdrawing (donating) degree.[39] For example, ring closure proceeds when this group is a chlorine, bromine, nitrile, ester and sulfide substituent. Conversely, no cyclisation is observed in the case of phenyl, trimethylsilyl, hydrogen or alkyl residues (Table 3).

Table 3. σ_I values for representative groups.

	Br	Cl	CN	CO_2Me	MeS	Ph	TMS	H	Alkyl
σ_I	0.47	0.47	0.57	0.32	0.30	0.12	−0.11	0.0	−0.01

Conclusion

In summary, we have reported a unique, efficient and connective reaction leading to highly functionalised benzofurans in good to excellent yields. Starting from *o*-hydroxyphenones, the corresponding *Z*-chloromethylene furans are initially obtained. These intermediates rearrange promptly into the corresponding benzofuran carbaldehydes under mild acidic conditions (0.01 M H_2SO_4). To illustrate the synthetic potential of our new method, some biologically active benzofurans have been efficiently assembled. Several mechanistic investigations have been carried out, the results of which support our mechanistic hypotheses. An incursion into the use of other acetylenes showed that interesting structures, such as bi- or tricyclic lactones, could be readily constructed, even though in some cases, the yields were rather modest. Further investigations are on-going and the application of this methodology to other heterocyclic structures is being actively pursued. These results will be reported in due course.

Experimental Section

3-Methylbenzofuran-2-carbaldehyde (17): Potassium *tert*-butoxide (1.30 g, 11.4 mmol, 3.8 equiv) was added portionwise to a solution of 2-hydroxyacetophenone (0.37 mL, 3 mmol, 1 equiv) and vinylidene dichloride (0.34 mL, 4.2 mmol, 1.4 equiv) in THF (15 mL). After 4 h, water (20 mL) was added. The aqueous phase was neutralised with diluted sulfuric acid. The aqueous layer was extracted with dichloromethane (3×20 mL). The organic phase was dried, filtered and concentrated. The crude mixture was dissolved in dichloromethane (100 mL) and aqueous sulfuric acid (100 mL, 0.01 M) was added. After 16 h under vigorous stirring, the aqueous layer was extracted with dichloromethane (2×60 mL). The organic layer was dried, filtered and concentrated. The crude mixture was then purified over silica gel yielding **17** as a yellow solid (0.465 g, 2.90 mmol, 97%). R_f = 0.64 (petroleum ether/ethyl acetate 5:1); m.p. 62 °C; ^{1}H NMR (300 MHz): δ = 9.94 (s, 1H), 7.60 (m, 1H), 7.45 (m, 2H), 7.27 (m, 1H), 2.53 ppm (s, 3H); ^{13}C NMR (75 MHz): δ = 179.5, 155.2, 148.0, 129.2, 128.5, 123.5, 121.7, 112.3, 8.2 ppm; MS (CI): *m*/*z*: 159.8; IR (neat): $\tilde{\nu}$ = 3310, 3067, 3036, 2920, 2862, 1661, 1612 cm^{-1}; elemental analysis calcd (%) for $C_{10}H_8O_2$: C 74.99, H 5.03; found: C 75.05, H 4.64. Other benzofurans were similarly prepared. For full details see the Supporting Information.

Acknowledgements

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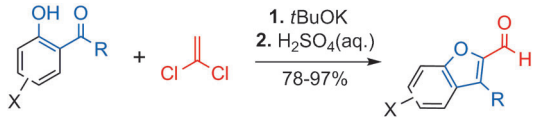
Heterocycles



Smooth operator: A unique, efficient and connective reaction is found to lead to highly functionalised benzofurans in good to excellent yields (see scheme). The key intermediate, a chloromethylene furan, smoothly rearranged into the corresponding benzofuran carbaldehyde under acidic conditions. Mechanistic investigations have been performed and several biologically active benzofurans have been synthesised.