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Alternative Coupling Reaction with Unactivated Furan Derivatives

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Treatment of various dienimides in the presence of a Lewis acid and (trimethylsiloxy)furan leads to the corresponding aniline furan-2(5*H*)-ones. The same treatment with furan yields a triaryl product and, surprisingly, a byproduct with a pentacyclo[5.4.0.0.0.0]undecane main core. The formation of this birdcage system containing nine stereogenic centres was produced with complete diastereoselectivity.

Introduction

Formation of novel C–C bonds in chemical synthesis is still a major challenge, especially in the coupling of two aromatic units as an avenue to biaromatics or to introduce an alkyl moiety onto an aromatic unit. These transformations have received attention due to the large number of natural compounds that incorporate these systems,[1] the use of axially chiral biaryls as ligands in asymmetric reactions[2] and the potential of bi- and polyaryls in materials chemistry and nanotechnology.[3] Different strategies have been developed to construct such systems; the first practical methods involve the Ullmann reaction[4] and variants thereof.[5] The scope of these transformations was greatly extended with the advent of nickel-[6] and, especially, palladium-mediated[7] reactions. Moreover, the development of new, efficient and environmentally benign methods for aryl–aryl or aryl–alkyl coupling remains an active field of research.[8] In this connection, techniques for the direct coupling of aromatic rings, that is, one technique that eliminates the need to prepare halogen or metal derivatives of the aryl fragments prior to their actual union, would be quite useful. New developments using hypervalent iodine reagents have recently been developed; important aspects of these reagents are their low toxicity compared to heavy metals and their abilities to directly achieve cross coupling of unfunctionalised arenes.[9] Ongoing work in our laboratory required rapid access to compounds of type **3** (Figure 1).

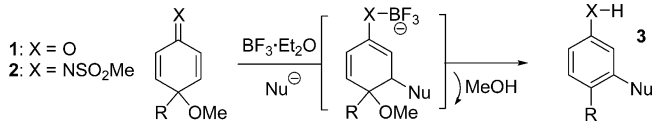

Figure 1. Possible avenue to compounds **3**.

Results and Discussion

Compounds such as **1** (X = O) or **2** (X = NSO_2Me) are easily synthesized by the oxidation of the corresponding phenols[10] and sulfonamides[11] with diacetoxyiodobenzene (DIB)[12] in methanol. These transformations produce desired compounds **1** and **2** in high yield (71–89%). This method provides easy and efficient access to dienones or dienimides. In addition, another hypervalent iodine reagent such as phenyliodine bis(trifluoroacetate) (PIFA)[12] can promote such transformations. First, we investigated the reactivity of compound **2** as a Michael acceptor. Although the behaviour of such dienones[13] has already been determined, a similar transformation on dienimides is poorly developed; only a few examples of Diels–Alder transformations have been related.[14] The differences in reactivities between dienones and dienimides were compared by oxidation of *para*-cresol and its mesylamide analogue **7** with DIB in ethylene glycol to produce alcohols **5**[13c,13f] and **8**. At this point, the behaviour of these alcohols in an intramolecular Michael process to produce bicycles **6** and **9** was compared (Scheme 1).

It has been observed that the cyclisation of intermediate **8** occurs faster than that of **5**. In addition, compound **8** is too reactive to be isolated. On the basis of this observation, we deduced that dienimide **8** seemed to be a very good Michael acceptor. Moreover, a diastereoselectivity of 2:1 for the double bond *cis* to the methanesulfonyl group was ob-

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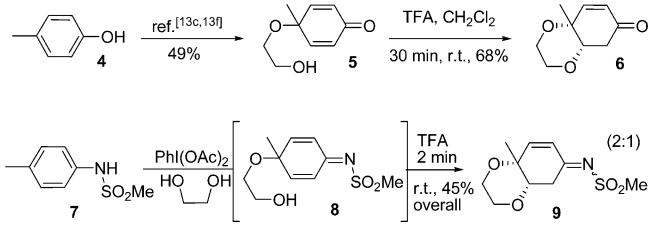


Scheme 1. Intramolecular Michael addition.

served.[15] An indication for understanding the diastereoselectivity observed is provided by ^{1}H NMR spectroscopy; indeed, the hydrogen atom close to the methanesulfonyl group in compounds **2** or **9** has a higher chemical shift than that of the hydrogen atom *trans* to the sulfonyl group (close to 1 ppm difference). A withdrawing effect generated by the *cis*-sulfonyl group may explain the diastereoselectivity observed. The behaviour of such structures is poorly developed, probably due to the difficulty in synthesizing them. The oxidative process[11] is currently the best method for producing such cores (Figure 2).

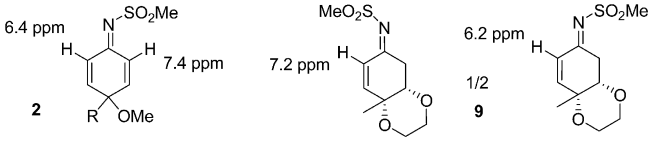
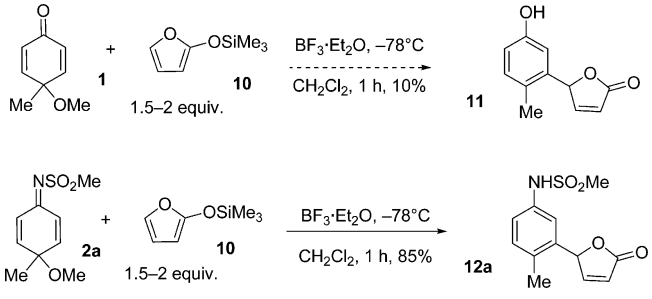


Figure 2. ^{1}H NMR chemical shift.

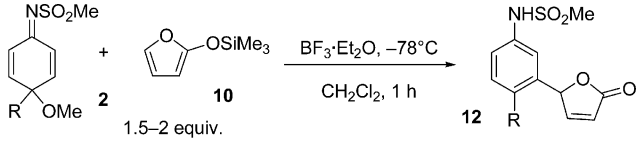
To develop a strategy for the rapid generation of structures such as **3** through a tandem Michael–aromatisation process, furan derivatives (1.5–2 equiv.) were used. It should be noted that such processes would require only the elimination of methanol as a byproduct. Although the reaction failed with dienone **1**, trace amounts of wanted compound **11** were isolated. However, we were pleased to observe the formation of desired compound **12** in good yield from dienimide **2**. This result demonstrates that the sulfonamide group appears to be a more efficient Michael acceptor than its oxygenated analogue (Scheme 2).



Scheme 2. Dienone vs. sulfonamide.

To exemplify this transformation, different dienimides such as **2** were treated under the same conditions. A summary of representative experiments with (trimethylsiloxy)-furan[16] **10** appears in Table 1.

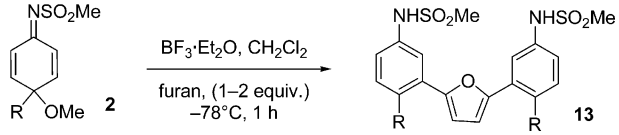
Table 1. A novel Michael-rearomatisation tandem process.



Entry	R	Yield [%]
a	Me	85
b	Et	82
c	*n*Pr	81
d	*n*Bu	90
e	$CH_2CH_2OTBDMS$	72
f	CH_2OH	42
g	CH_2CH_2OMs	79

This reaction tolerates functionalities such as a protected alcohol (Table 1, Entry e) or a mesylate (Table 1, Entry g) on the aliphatic side chain, suggesting that the new process may tolerate a range of spectator functional groups. The reaction with a free methyl alcohol (Table 1, Entry f) occurs in lower yield to produce the fragile benzyl alcohol functionality. This alternative cross-coupling reaction also occurs with furan (1–2 equiv.). It should be noted than furan is a poorer nucleophile than compound **10**. Under these conditions, we observed the formation of dimer **13** resulting in the bis(arylation) of furan; only a small amount of monoaddition was observed (≈5%). This result can be explained if we consider that the monosubstituted furan derivative is more electron rich than regular furan and reacts faster with a second molecule of dienimide **2**. A summary of representative experiments appears in Table 2.

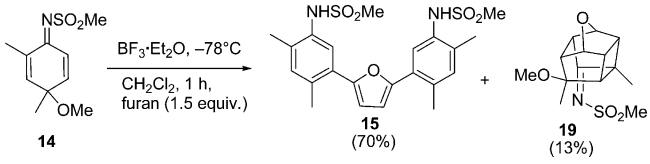
Table 2. Formation of bicyclic compound **13**.



Entry	R	Yield [%]
a	Me	71
b	Et	64
c	*n*Pr	60
d	*n*Bu	62
e	$CH_2CH_2OTBDMS$	62
g	CH_2CH_2OMs	61
h	CH_2CO_2Me	43

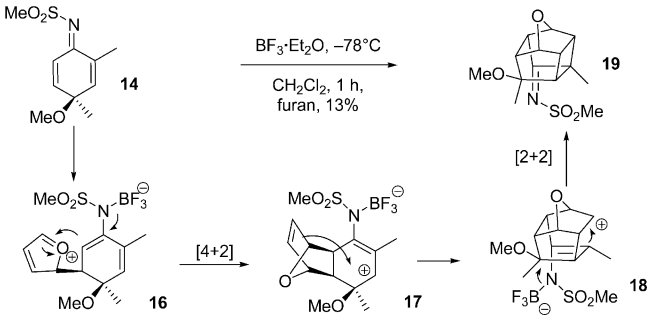
This reaction in the presence of furan also tolerates functionalities such as a protected alcohol (Table 2, Entry e), a mesylate (Table 2, Entry g) or an ester (Table 2, Entry h) on the aliphatic side chain, suggesting that the new process may tolerate a range of spectator functional groups. This method is a novel benign avenue to the formation of C–C bonds through a C–H/C–H cross-coupling reaction. This result suggests that this reaction could be performed with different electron-rich furan derivatives. In this process, the

electrophilic character of dienimide **2** is trapped by an electron-rich furan derivative in a manner consistent with electrophilic substitution of furans. This transformation also succeeds with polysubstituted dienimide **14** in the presence of furan (Scheme 3).



Scheme 3. Polysubstituted dienimide.

The reaction with compound **14** leads to intriguing by-product **19** in 13% yield. The structure produced contains a pentacyclo[5.4.0.0.0.0]undecane[17] main core. Formation of such a compound can be explained if we consider that a double formal cycloaddition tandem process occurred. Indeed, we assume that intermediate **16** was trapped by the mesylenamide group to generate **17** through a formal [4+2] cycloaddition. The Lewis acid should activate the remaining enimide functionality that would be trapped by the double bond of the dihydrofuran moiety to generate species **18**, assimilated into a Prins reaction. Intermediate **18** would be intercepted by the mesylenamide segment to produce **19** through a formal [2+2] cycloaddition. This tandem process reaction yields unique structure **19** containing nine stereogenic centres produced in only one step and with complete diastereoselectivity verified by NOE NMR spectroscopic analysis (Scheme 4).



Scheme 4. Formation of a birdcage system.

Conclusions

In summary, a practical and new method for the formation of C–C bonds between dienimides and furan derivatives under metal-free and benign conditions to produce functionalised *N*-aryl methanesulfonamides is now available. The transformation provides new strategic opportunities in the chemical synthesis of nitrogenous substances, and the results of ongoing investigations with different aromatic derivatives, mild nucleophilic reagents and their applications will be disclosed in due course.

Experimental Section

General Procedure for the Oxidative Process: To a stirred solution of sulfonamide (0.5 mmol) in methanol (5 mL) at 20 °C was added $PhI(OAc)_2$ (DIB, 0.6 mmol, 1.2 equiv.) dissolved in methanol (2 mL) over 10 s. The reaction was stirred for 10 min, concentrated and then purified by chromatography (hexane/ethyl acetate as required).

General Procedure for the Coupling Process with 2-(Trimethylsiloxy)-furan: To a stirred solution of compound **2** (0.1 mmol) and 2-(trimethylsiloxy)furan (0.15–0.2 mmol, 1.5–2 equiv.) in dry dichloromethane (2 mL) at –78 °C was added $BF_3{\cdot}OEt_2$ (0.2 mmol, 2 equiv.). The mixture was stirred and kept at –78 °C until the reaction was complete as indicated by TLC (1–1.5 h) and then quenched with saturated aqueous $NaHCO_3$ (5 mL). The aqueous phase was extracted with EtOAc (3 × 8 mL), and the combined organic layer was washed with brine (2 × 5 mL), dried with Na_2SO_4 and concentrated. The crude product was purified under vacuum then purified by chromatography (hexane/ethyl acetate as required). The compound requires rapid purification to avoid potential isomerisation of the double bond.

General Procedure for the Coupling Process with Furan: To a stirred solution of compound **2** (0.1 mmol) and furan (0.2 mmol, 2 equiv.) in dichloromethane (2 mL) at –78 °C was added $BF_3{\cdot}OEt_2$ (0.2 mmol, 2 equiv.). The mixture was stirred and kept at –78 °C until the reaction was complete as indicated by TLC (1–1.5 h) and then quenched with saturated aqueous K_2CO_3 (3 mL). The aqueous phase was extracted with EtOAc (3 × 8 mL), and the combined organic layer was washed with brine (2 × 5 mL), dried with Na_2SO_4 and concentrated. The crude product was purified by chromatography (hexane/ethyl acetate as required).

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data for all new compounds along with copies of the ^1H and ^{13}C NMR spectra.

Acknowledgments

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