A brief synthesis of β-iodofurans

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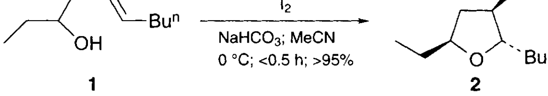
5-*Endo*-dig iodocyclisations of alk-3-yn-1,2-diols 4, followed by *in situ* dehydration, lead to good yields of β-iodofurans 5, which can subsequently be converted into a wide range of derivatives 6–13, using transition metal-catalysed coupling reactions or halogen-metal exchange.

The recent successful development of highly stereoselective methods for the overall 5-*endo*-trig cyclisation of homoallylic alcohols (*e.g.* **1**) leading to tetrahydrofurans (*e.g.* **2**) has opened up a new approach to these ubiquitous targets.[1] Although seemingly 5-*endo*-trig cyclisations, usually disfavoured processes, the activating effect of the iodonium intermediate suggests that these are not true exceptions to Baldwin's rules.[2] We were intrigued by the possibility that similar cyclisations involving related homoprop-2-ynylic alcohols could also be successful, especially as these would be, formally, 5-*endo*-dig processes which, in contrast, are favoured reactions.[2] We further reasoned that, if an additional leaving group were present, the intermediate dihydrofurans, if formed, could then be converted into the corresponding furans. Here we report the successful outcome of our first experiments in this area.

A particularly brief way in which one group of potential substrates for this type of cyclisation could be obtained relies on the regioselective dihydroxylation of a conjugated enyne **3**. The utility of this transformation has recently been highlighted in a further exemplification of the versatility of the AD-Mix procedure.[3] Of course, for our purposes we did not require homochiral substrates and therefore used the standard OsO_4–4-methylmorpholine oxide (NMO) method[4] to convert the enynes **3**, which are readily accessible as either (*E*)- or (*Z*)-isomers, most notably by using a variety of transition metal-catalysed sp–sp^2 coupling reactions,[3] into the requisite alkyndiols **4**. We were pleased to find that upon exposure to 3 equiv. of iodine in acetonitrile, containing 3 equiv. of sodium hydrogencarbonate for 2–12 h at ambient temperature, these were smoothly converted into the iodofurans **5**. All yields shown refer to pure, isolated material. Both alkyl and aryl substituents can be incorporated at either α-position of the furans **5**. Attempts to cyclise a 3,4-dihydroxyalk-1-yne were unsuccessful, as the terminal alkyne function underwent rapid addition of iodine leading to the corresponding 1,2-diiodoalkene. We presume that the mechanism involves a 5-*endo*-dig cyclisation to a 3-hydroxy-4-iodo-2,3-dihydrofuran which rapidly undergoes dehydration to the corresponding iodofuran **5**; efforts to observe this putative intermediate were not successful. Interestingly, *syn*-isomers, derived from (*E*)-isomers of the enynes **3**, underwent cyclisation more rapidly (~2 h) than the corresponding *anti*-diastereoisomers (~12 h) of the alkyndiols **4**; isolated yields were, however, comparable. This phenomenon may be associated with a more favourable transition state geometry.[1]



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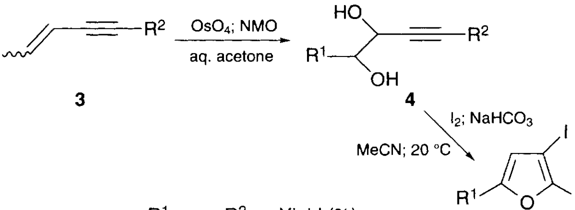
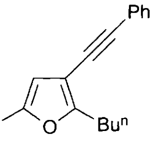


3 **4** **5**

	R^1	R^2	Yield (%)	
a	Me	Bu	65	[from (*Z*)-3]
b	Me	Ph	88	[from (*Z*)-3]
c	Ph	Bu	71	[from (*E*)-3]
d	Ph	Ph	60	[from (*E*)-3]
e	CO_2Me	Ph	47	[from (*E*)-3]

There is still considerable interest in the development of novel approaches to furans in general; some of these recently reported routes feature both 5-*endo*- and 5-*exo*-dig cyclisation modes, generally triggered by basic conditions.[5] In contrast to many other five-membered heteroaromatic systems, β-halofurans are especially difficult to prepare,[6] which is unfortunate as they offer considerable potential for further elaboration, particularly using the many, more recently developed methods for coupling such sp^2 centres.[7] We have illustrated the potential of the present brief approach to β-iodofurans **5** by carrying out a selection of such coupling reactions using the iodofurans **5c** and **5d**. For example, the Sonogashira method [$(Ph_3P)_4Pd$, Et_2NH, CuI, 20 °C, 12 h][8] featuring the direct coupling of a terminal alkyne, can be used to prepare the alkynylfurans **6** and **7** in 60 and 95% yields respectively. Stille couplings [$(Ph_3P)_2PdCl_2$, DMF, 40 °C, 12 h][9,10] with vinyl- or *p*-tolyltributylstannane gave similarly good yields (66 and 57% respectively) of the expected homologous furans **8** and **9**; in contrast, couplings using 2-(tributylstannyl)thiophene gave a lower yield (< 30%) of the thienofuran **10**, when $(Ph_3P)_4Pd$ was used as the catalyst. Carbonylation of iodofuran **5d** using $(Ph_3P)_2PdCl_2$ as catalyst followed by trapping with *p*-tolyltributylstannane[11] gave the acylated furan **11** in an unoptimized yield of 30%. The classical method of halogen-metal exchange can also be used to homologate β-halofurans, provided the temperature of the reaction is kept low to prevent ring opening. In the case of iodofuran **5d** lithiation using butyl lithium in tetrahydrofuran at −78 °C, followed by trapping with either *N*,*N*-dimethylformamide or iodomethane, gave the 3-substi-



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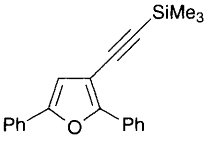

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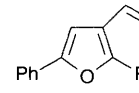

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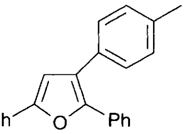

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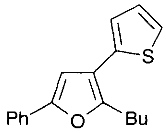

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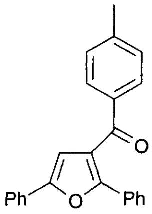

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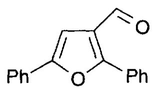

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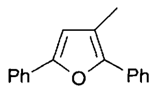

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tuted derivatives **12** and **13** in 80 and 92% isolated yields respectively.

We gratefully acknowledge support of this work from the Royal Society by a Leverhulme Senior Research Fellowship (to D. W. K.) and by the EPSRC (Postdoctoral Fellowship to S. P. B.).

References

1 S. H. Kang and S. B. Lee, *Tetrahedron Lett.*, 1993, **34**, 1955 and 7579; J. M. Barks, D. W. Knight and G. G. Weingarten, *J. Chem. Soc., Chem. Commun.*, 1994, 719; J. M. Barks, D. W. Knight, C. J. Seaman and G. G. Weingarten, *Tetrahedron Lett.*, 1994, **35**, 7259; B. H. Lipshutz and T. Gross, *J. Org. Chem.*, 1995, **60**, 3572; Y. Landais, D. Plancheuault and V. Weber, *Tetrahedron Lett.*, 1995, **36**, 2987 and references cited therein.

2 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.

3 K.-S. Jeong, P. Sjö and K. B. Sharpless, *Tetrahedron Lett.*, 1992, **33**, 3833. For an extensive review of the AD-Mix methodology, see H. C. Kolb, M. S. Van Nieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.

4 V. VanRheenen, R. C. Kelly and D. Y. Cha, *Tetrahedron Lett.*, 1976, 1973; M. Schröder, *Chem. Rev.*, 1980, **80**, 187.

5 See, for example, J. A. Marshall and W. J. DuBay, *J. Org. Chem.*, 1993, **58**, 3435; J. M. Aurrecoechea and M. Solay-Ispizua, *Heterocycles*, 1994, **37**, 223; J. A. Marshall and C. E. Bennett, *J. Org. Chem.*, 1994, **59**, 6110; A. R. Katritzky and J. Li, *J. Org. Chem.*, 1995, **60**, 638, and references cited therein. For a recent review, see T. L. Gilchrist, *Contemp. Org. Synth.*, 1994, 205.

6 For recent contributions, see D. Obrecht, *Helv. Chim. Acta.*, 1989, **72**, 447; Z. Z. Song and H. N. C. Wong, *Annalen*, 1994, 29.

7 D. W. Knight, *Compr., Org. Synth.*, 1991, **3**, 481.

8 K. Sonogashira, *Compr., Org. Synth.*, 1991, **3**, 521.

9 D. R. McKean, G. Parrinello, A. F. Renaldo and J. K. Stille, *J. Org. Chem.*, 1987, **52**, 422.

10 For similar couplings with bromofurans, see G. Karminskizamola, J. Dogan, M. Bajic, J. Blazevic and M. Malesevic, *Heterocycles*, 1994, **38**, 759.

11 J. K. Stille, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 508.

Received, 16th February 1996; Com. 6/01157H