A new ring enlargement reaction of γ-lactones to seven-membered cyclic ethers *via* intramolecular *endo*-mode cyclisation of the ω-hydroxy allenyl ketone intermediates *in situ*

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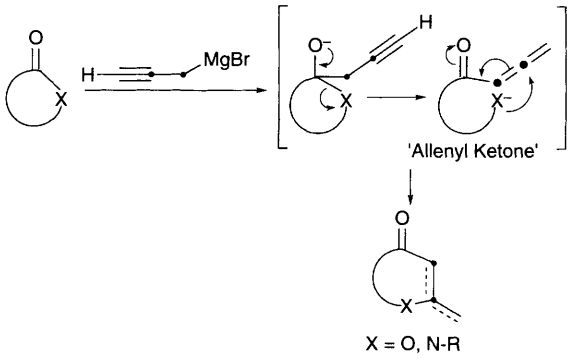
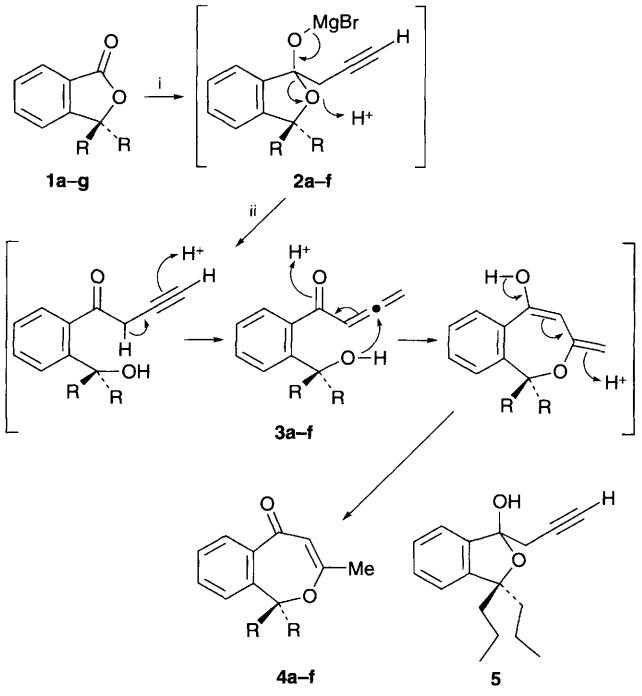
Phthalides 1a–f were treated with prop-2-ynylmagnesium bromide followed by treatment with 20% HCl in one pot to give the corresponding seven-membered cyclic ethers, benzoxepins 4a–f.

Recently, the synthetic development of heterocyclic compounds utilising the allenic systems have been extensively studied.[1] Our recent research has been focused on the development of new cyclisation reactions utilising the allenyl ketone system.[2] We have reported new cyclisation reactions for five- to eight-membered carbocyclic compounds[2a,b] and spiro[4.5]decatriene and spiro[5.5]undecatriene diones[2c] on the basis of intramolecular *endo*-mode ring closure at the sp carbon of the allenyl ketone moiety. Thus, we applied the *endo*-mode cyclisation method to heterocyclic ring expansion reactions[3] according to the methodology based on a hypothetic pathway as shown in Scheme 1. This heterocyclic ring expansion procedure involves nucleophilic addition of prop-2-ynylmagnesium bromide onto the lactone or lactam carbonyl carbon releasing the X^- (*i.e.* O^-, NR^-) group, followed by its nucleophilic attack upon the sp carbon atom of the resulting allenyl ketone intermediate. Two carbon atom-expanded heterocycles can then be formed.



Scheme 1



Scheme 2 *Reagents and conditions*: i, prop-2-ynylmagnesium bromide (1 mol dm^{-3}, 1.2 mol equiv.), THF, 0 °C, 5 min; ii, 20% HCl, 0 °C, 5 min

Here, a new ring expansion reaction of γ-lactones, phthalides, to seven-membered cyclic ethers is described (Scheme 2). To a solution of 3,3-dipropylphthalide **1d** (218.3 mg, 1 mmol)† in anhydrous THF (20 ml) was added a diethyl ether solution of prop-2-ynylmagnesium bromide (1 mol dm^{-3}, 1.2 ml, 1.2 mmol)[2a] at 0 °C with stirring under N_2. After being stirred at 0 °C for 5 min, the reaction mixture was treated with 20% HCl (5 ml) for 5 min, then submitted to the usual workup to afford directly the seven-membered cyclic ether **4d** (201 mg, 78% yield) as colourless needles.‡ Other phthalides **1a–c**, **e**, **f**† were similarly treated with 1.2 mol equiv. of prop-2-ynylmagnesium bromide followed by treatment with 20% HCl to furnish the corresponding seven-membered cyclic ethers **4a–c**, **e**, **f**.‡ Similar treatment of 3,3-diphenylphthalide **1g** resulted only in its recovery (86%). Interestingly, the magnesium-free compound **5**, obtained by quenching the prop-2-ynyl adduct **2d** with water, was converted to **4d** in 92% yield on treatment with 20% HCl in THF. Thus, the expeditious ring enlargement of the γ-lactones **1a–f** to the seven-membered cyclic ethers **4a–f** can be rationalized in terms of a tandem reaction pathway *via* the acid-promoted ring-opening of hemiacetals **2a–f** followed by intramolecular ether-ring formation in the resultant ω-hydroxy allenyl ketones **3a–f**. The structures of all benzoxepin derivatives **4a–f** were readily confirmed by their characteristic spectroscopic data.§

These new benzoxepins **4a–f** are interesting from the view point of the similar structure of pharmacologically active benzazepines.[5].

Footnotes

† All substituted phthalides were readily prepared by treatment of commercially available phthalic anhydride with 2 mol equiv. of the corresponding alkyl (or phenyl)magnesium bromide according to the reported procedure.[4]

‡ **4a**: 45%, pale yellow oil; **4b**: 69%, pale yellow oil; **4c**: 86%, pale yellow oil; **4d**: 78%, colourless needles (mp 95 °C) from CH_2Cl_2–hexane; **4e**: 48%, colourless needles (mp 90–91 °C) from CH_2Cl_2–hexane; **4f**: 49%, pale yellow oil.

§ *Selected data* for **4a–f**: [IR ($CHCl_3$) ν 1619–1645 cm^{-1} (α,β-unsaturated carbonyl); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.05–2.54 (s, 3 H, allylic Me), δ 5.62–5.76 (s, 1 H, =CH– proton)].

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