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6-*exo* versus 7-*endo* iodolactonizations of 2-(alkynyl)phenylacetic acids

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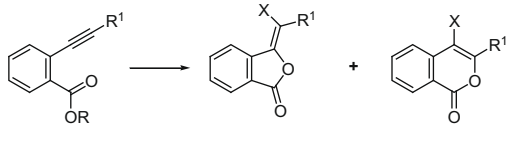
ABSTRACT

Exposure of 2-alkynylphenylacetic acids to excess iodine in acetonitrile containing anhydrous potassium carbonate delivers good yields, either of the corresponding isochroman-3-ones or benzo[*d*]oxepin-2(1*H*)-ones, depending upon the alkyne substituent: when this is alkyl, the former 6-*exo* products dominate, otherwise the 7-*endo* products are formed largely or, more often, exclusively.

Baldwin's rules have provided sound guidance in the design and rationalisation of cyclisation processes, since these were first reported.[1] While there are arguably no or, at least, very few exceptions to these principles, there are occasional ambiguities amongst some pairs of 'favoured' cyclisation pathways in various combinations of substrate and cyclisation method. An example of this is in cyclisations of 2-(alkynyl)benzoic acids and esters **1**, which can lead either to the ylidenephthalides **2** by a 5-*exo*-dig process or to the isocoumarins **3** by a 6-*endo*-dig cyclisation; in many cases, mixtures of both products are obtained (Scheme 1).

Thus, during electrophile-driven iodocyclisations of the acids [**1**; R = H][2] or esters [**1**; R = alkyl][3] using iodine, mixtures of the two products [**2** and **3**; X = I] were generally obtained, although use of the more reactive iodine monochloride as an iodonium source gave very largely or exclusively the 6-*endo* products [**3**; X = I]. Of course, the successful use of iodonium ions to trigger such cyclisations leaves an iodine atom attached to the product(s), which is usually amenable to further manipulation, especially using one of the myriad of modern palladium-catalysed coupling reactions, as has been demonstrated in the foregoing reports.[2,3] These palladium catalysts can even be utilized to induce these very types of cyclisation, when a preponderance of the 5-*exo* ylidenephthalides [**2**; X = H] is obtained.[4] Similarly, starting with the tributylstannyl ester of 2-iodobenzoic acid, sequential Sonogashira coupling and Pd-catalysed cyclisation follows a 5-*exo* pathway to give a stannyl ylidenephthalide.[5] In contrast, use of silver-based catalysts tends to favour 6-*endo* cyclisation to the isocoumarins [**3**; X = H], although ylidenephthalides are occasionally the major products in cyclisations, which appear to be both catalyst- and substrate-dependent.[6] In the latter report, copper catalysis is also implicated in such cyclisations, but to give mixtures of products; a later report suggests that 6-*endo* products are strongly favoured by copper(I) catalysts in the presence of acid (TFA) and under microwave conditions.[7] Much simpler acidic or basic catalysts can also be employed to activate the benzoic acid derivatives **1** towards cyclisation: an early study of acid-catalysed cyclisations indicates that the 5-*exo* ylidenephthalide products may be the kinetic isomers, which subsequently isomerise to the 6-*endo* isocoumarins, although in this particular example, a suitably positioned carboxylic acid group may well have provided assistance.[8] More recent studies, however, while confirming that acid catalysis leads to isocoumarins and base-catalysis to the ylidenephthalides, strongly suggest this is all due to a mechanistic change: under acidic conditions, the key is protonation of the carboxylic acid group, whereas under basic conditions, it is its deprotonation which is key.[9]

It was against this background that we wondered how the homologous alkynylphenylacetic acids and derivatives might behave under these cyclisation conditions, particularly because, as in the foregoing cases, both cyclisation modes, 6-*exo*-dig and 7-*endo*-dig, are favoured according to Baldwin.[1] Further, if the latter pathway were to be followed, potentially useful benzo-oxepinone systems would be generated of a type, which are not common in the literature. Indeed, only two very recent reports detail any activity in this area of cyclisation methodology. A combination of a palladium catalyst and potassium hydroxide (DMF, 60 °C, 16 h) is necessary to give decent isolated 42–82% yields of the benzazepinones **5** when the substituent 'R' is an alkyl group. In contrast to this 7-*endo* pathway, the corresponding (*E*)- and (*Z*)-isomers of an unstable 3-isoquinolinone **6**, the product of 6-*exo* cyclisation, are formed from the 2-(phenylethynyl) derivative [**4**; R = Ph] (Scheme 2).[10]



1 **2** [5-*exo*] **3** [6-*endo*]

Scheme 1.

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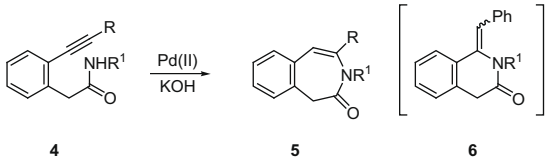


4 5 6

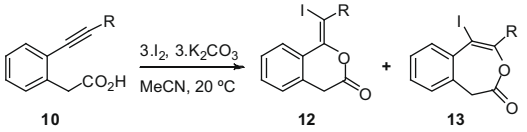
Scheme 2.

In a search for alternative transition metal catalysts for carrying out the cyclisations shown in Scheme 1, treatment of the acids [**1**; R = H] with 10 mol % gold(I) chloride and potassium carbonate in acetonitrile was found to generally give mixtures of both possible products [**2** and **3**; R = X] usually with a preponderance of the 5-*exo* when such was observed, whereas exposure of the corresponding methyl esters [**1**; R = Me] to gold(III) chloride in wet acetonitrile gave exclusively the 6-*endo* products **3**.[11] Presumably, water is necessary to assist in hydrolysis of the intermediate methyl oxonium species and to provide protons for a final exchange with the gold(III). In contrast, exposure of 2-(phenylethynyl)acetic acid **10** to the gold(I) system gave mainly the 6-*exo* products, ylidenelactones, while gold(III) catalysts were inactive. One example, when the alkyne substituent was *n*-propyl, gave a preponderance (9:1) of the 7-*endo* product, a benzo-oxepinone (see below). We were therefore intrigued to find out how such 2-(alkynyl)phenylacetic acids would behave under iodolactonization conditions.

The starting materials were readily prepared from commercial 2-iodophenylacetic acid. Homologation of the derived methyl ester **7** by Sonogashira couplings[12] with various 1-alkynes **8**, using the excellent, cheap and convenient procedure introduced by Batchu and co-workers,[13] followed by saponification delivered the necessary acids **10** (Scheme 3). In cases where the required aryl alkyne was not commercially available, this was prepared directly from the corresponding benzaldehyde using the Ohira-Bestmann α-diazophosphonate in methanolic potassium carbonate.[14] As another option, a more conventional Sonogashira coupling between iodo-ester **7** and trimethylsilylacetylene followed by desilylation delivered the terminal alkyne **11** in 83% yield for the two steps. Subsequently, a second Sonogashira coupling with an aryl iodide, again using the Batchu procedure, and hydrolysis provided an alternative route to the precursors **10**.

The various alkyne substituents employed are detailed in Table 1, in which the results of our iodolactonizations of the 2-(alkynyl)phenylacetic acids **10** are summarized. Following a number of trial reactions, acetonitrile appeared to be the optimum solvent, in the presence of 3 equiv each of iodine and anhydrous potassium carbonate. The requirement for three equivalents of iodine is a typical feature of such cyclisations; if less is used, cyclisations are usually incomplete. As yet, this phenomenon has not been satisfactorily explained.[15] As shown in Table 1, the cyclisations resulted in useful levels of regioselection, with the major products being isolated in reasonable yields following column chromatography. Use of sodium hydrogen carbonate as base resulted in slightly lower regioselectivities.

Table 1
Iodolactonizations of 2-(alkynyl)phenylacetic acids **10**



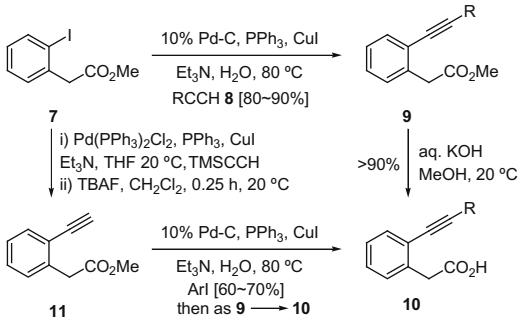
10 12 13

Entry	R	Time[a]	Yield	*exo*/*endo* ratio	^{13}C NMR ppm[b]	
					3-CH_2	C=O
a	*n*-Bu	24	82	81:19	38.2	166.9
b	CH_2OH	24	71	93:7	36.2	166.0
c	C_6H_5	24	67	76:24	37.2	166.1
d	4-$NO_2C_6H_4$	1	—			
e	4-$MeOC_6H_4$	3	81	5:95	41.2	167.5
f	3,4-$CH_2OCH_2C_6H_3$	2	66	<5:>95	41.0	168.0
g	2,3,4-$(MeO)_3C_6H_2$	0.2	72	<5:>95	41.0	168.9

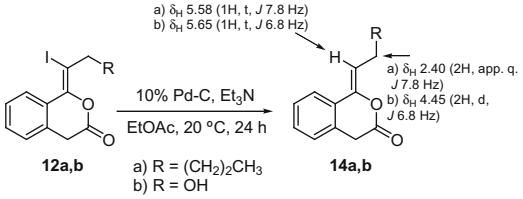
[a] In hours.
[b] Chemical shift (400 MHz, $CDCl_3$) of the major isomer.

Initial results using the butyl-substituted acid **10a** gave two isomers in a ratio of 4.1:1, but the identity of the products was far from clear. In contrast, the propargyl alcohol derivative **10b** gave almost a single isomer. In both cases, all spectroscopic and analytical data were consistent with either of the isomeric structures **12** and **13**. Very fortunately, it proved to be possible to selectively remove the iodine atom from these two products by hydrogenolysis to give high yields of the de-iodo derivatives, the ^{1}H NMR spectra of which, when obtained for dilute solutions in deuteriochloroform at 400 MHz, clearly showed these to be derived from the 6-*exo* isochromanone isomers **12a** and **12b** (Scheme 4); it is inconceivable that such resonances could arise from the alternative regioisomers **15a,b**.[16]

Hence, it was concluded that both the alkyl-substituted precursors **10a,b** had undergone selective 6-*exo*-dig iodolactonizations to give the isochromanones **12a,b**. The likelihood of an *anti*-addition mechanism rather favoured formation of the (*E*)-isomers shown, as did the identity of the hydrogenolysis products **14a,b** when compared with previously reported samples.[11] However, there is a slight uncertainty regarding this aspect. The major or exclusive products derived from the remaining substrates **10c–g** (Table 1), all of which have an aryl substituent positioned at the terminus of the alkyne group differed from these two initial products. Although infrared carbonyl stretching data were inconclusive, there was a distinct pattern in the chemical shifts associated with the 3-methylene and carbonyl resonances in the ^{13}C data (see Table 1). While the two alkyl-substituted products **12a,b** showed methylene resonances around 37 ppm and carbonyl carbons

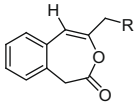


Scheme 3.



Scheme 4.

around 166–167 ppm, these latter products **13e–g** showed ranges of ~41 and 168 ppm for the corresponding resonances. Hence, it was concluded that these were the benzo[*d*]oxepinones **13e–g**, arising by a 7-*endo*-dig pathway. These conclusions were also consistent with some appropriate data shown by similar compounds obtained by Marchal et al. during their work on the related gold-catalysed cyclisations.[11] These data were also consistent with the probable formation of small amounts of the alternative ring sizes in each example. Thus, although partly obscured in the initial iodinated product **12a**, the ^{1}H NMR spectrum of the hydrogenolysis product **14a** displayed a distinct olefinic singlet centred on δ_H 6.21, which was assigned to the seven-membered ring product [**15**; R = C_3H_7].[11] The phenyl case **10c** appears to be an exception. Some further evidence was obtained by hydrogenolysis of the 4-methoxy derivative **12e,** which delivered a product **15** [R = 4-MeOC_6H_4] displaying an olefinic proton at δ_H 6.86, a position very similar to that quoted by Marchal et al.[11] for the same compound. By contrast, the isomeric isochromanone is reported to show an olefinic resonance at δ_H 6.28, a clear difference. Unfortunately, other data (remaining ^{1}H and ^{13}C NMR data, m.p.s, ir) were closely similar and could not realistically be used for definitive assignments.

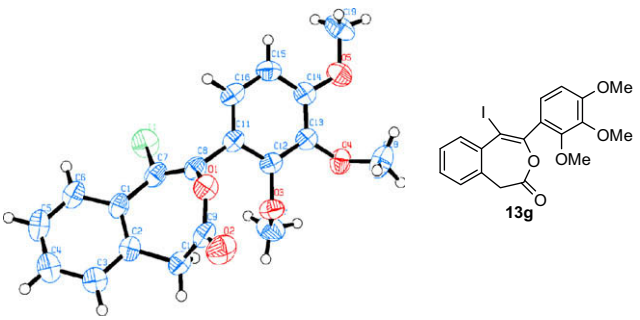


15

Final proof of the seven-membered ring structures **13** was obtained by X-ray crystallographic analysis of the 2,3,4,-trimethoxyphenyl product **13g**, the ORTEP diagram of which is shown in Figure 1.[17]

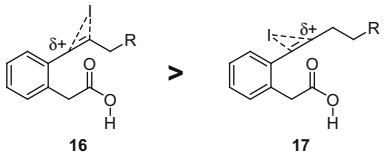
Hence, our conclusion is that iodolactonizations of 2-(alkynyl)phenylacetic acids **10** favour the 6-*exo* pathway to give isochromanones **12** when the alkyne substituent is alkyl, but the alternative 7-*endo* route leading to benzo[*d*]oxepinones **13** when the same substituent is aryl. This may possibly be explained by considering the process to involve a relatively late transition state. In the case of an alkyl-substituted intermediate, perhaps the mesomeric effect of the aryl ring (**16**) outweighs the inductive effect of the alkyl group (**17**) in stabilizing the developing electron-deficient carbon centre (Fig. 2).

The relatively poor level of stereoselection shown by the phenyl-substituted example **10c** may simply be due to the rather symmetrical nature of the intermediate **18**, together with the usual preference for an *exo* cyclisation mode over a competing *endo* pathway (Fig. 3). Participation by a *para*-methoxy group **19**, represented in extreme form by structure **20,** could override all other factors and explain the very high preference for formation of the 7-*endo*-dig products **13e–g**. Unfortunately, the related 4-nitro



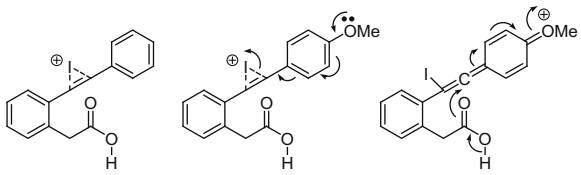
13g

Figure 1. ORTEP diagram of the 2,3,4-trimethoxybenzo[*d*]oxepinone **13g**.



16 **17**

Figure 2.



18 **19** **20**

Figure 3.

derivative **10d**, while reacting rapidly with iodine, failed to give meaningful products, a pity, as the product(s) arising could have contributed significantly to these ideas.

In any event, these examples indicate that this chemistry can be used to prepare the structural types **12** or **13** with often high regioselectivities, but only when the correct substituent is present on the alkyne terminus.

Acknowledgement

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16. For an alternative method for carrying out this selective deiodination, see Ref. 2a.
17. Compound **13g** crystallized from ethyl acetate/petrol, mp 157–159 °C. $C_{19}H_{17}IO_5$, M_r = 452.23, monoclinic, *P*21/*c*, *a* = 16.4140(6) Å, *b* = 11.5730(4) Å, *c* = 9.5930(3) Å, β = 98.675(2)°, *V* = 1801.43(11) Å^3, *Z* = 4, DX = 1.667 Mg m^{-3}, λ(Mo Kα) = 0.71073 Å, μ = 1.803 cm^{-1}, *F*(000) = 896, *T* = 296(2) K, crystal size = 0.40 × 0.35 × 0.20 mm^3, Reflections collected = 10,605, Independent reflections = 4009, 2676 with $F_o > 4(F_o)$, R_{int} = 0.0395, Final R_1 = 0.0402, wR_2 = 0.0836 for $I > 2\sigma(I)$, and R_1 = 0.0710, wR_2 = 0.0946 for all data.Data

were recorded on a Nonius Kappa CCD diffractometer equipped with an Oxford Cryosystem cryostat. The structure was solved by direct methods with additional light atoms found by Fourier methods using SHELX97 (SHELX97—Programs for Crystal Structure Analysis (Release 97-2). G.M. Sheldrick, Institüt für Anorganische Chemie der Universität, Tammanstrasse 4, D-3400 Göttingen, Germany, 1998.). Hydrogen atoms were added at calculated positions and refined using a riding model. Anisotropic displacement parameters were used for all non-H atoms; H-atoms were given isotropic displacement parameters equal to 1.2 or 1.5 times the equivalent isotropic displacement parameter of the atom, to which the H-atom is attached. The CIF file has been deposited at the Cambridge Crystallographic Deposit Centre with registry number CCDC 702984.