Pergamon

Tetrahedron Letters 43 (2002) 3849–3852

TETRAHEDRON LETTERS

Steric and electronic limitations for the Dötz benzannulation of aromatic alkynes

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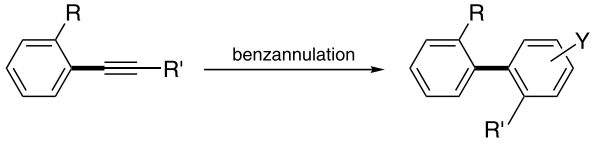
Received 28 January 2002; revised 25 March 2002; accepted 5 April 2002

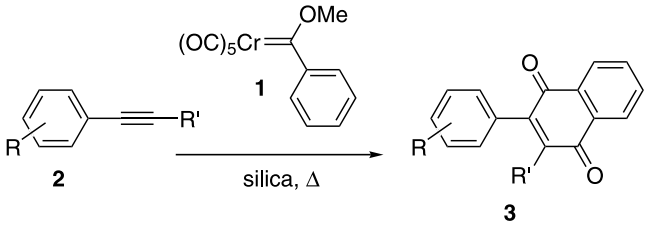
Abstract—As part of an investigation into a new strategy for biaryl synthesis, the Dötz benzannulation of a series of substituted aryl acetylenes was undertaken to determine possible steric and electronic effects exerted by the aryl group. In the *ortho* position it was found that methyl, methoxy, chloro and *N*-amide substituents give moderate to good yields of product, whereas carbonyl derivatives and the nitro group are deleterious. © 2002 Published by Elsevier Science Ltd.

Hindered biaryl systems are unique molecular scaffolds which exhibit interesting properties due, in part, to atropisomerism around the aryl–aryl bond. Axially chiral biaryl compounds are an important constituent of many biologically active natural and unnatural products[1] and used as chiral ligands for asymmetric catalysis.[2] Probably the most powerful method of constructing a biaryl axis is through the direct coupling of two aryl groups.[3] Most commonly this has been achieved by transition metal catalysed cross coupling between an aryl electrophile and aryl nucleophile but the range of substrates is limited by the steric requirements of the system,[4,5] although this problem has been circumvented through ligand tuning by Buchwald.[6] We have been investigating an alternative and at present unconventional strategy for biaryl synthesis which relies upon the construction of the biaryl bond before the construction of the final aryl group (Eq. (1)).[7]



(1)

There are a number of benzannulations which could be applied to this reaction,[8] but we chose to assess the benzannulation by Fischer carbene complexes due to their widely reported efficiency at generating highly substituted benzenoid compounds with good regiochemical control and chemical yield in one step.[9] There have been studies detailing the steric and electronic requirements of the arylcarbene complex[10] and the alkyne,[11] but none specifically looking at the character of the aryl group of an aryl acetylene. There are only a few examples of benzannulations of aryl acetylenes leading to hindered biaryl systems.[7c] In order to investigate the scope of the proposed approach we have investigated the steric and electronic limitations with respect to the aryl group of a series of substituted aryl acetylenes in the Dötz benzannulation reaction.



(2)

Studies were carried out using readily available aryl Fischer carbene complex **1**[12] and a series of aryl acetylenes **2** (Eq. (2)). The acetylenes were synthesised by Sonogashira coupling reaction[13] between the requisite aryl halide and a terminal acetylene.[14] We found the water based system developed by Bumagin, Beletskaya and co-workers[15] to be superior to non-aqueous conditions[16] and to provide most of our simple aryl acetylenes **2** in good yield. The *ortho*-amide substituted **2l** could not be formed from the requisite halide so **2i** was treated with LDA in THF at −78°C to give **2l** in

Keywords: biaryls; alkynes; Dötz reactions; quinones.

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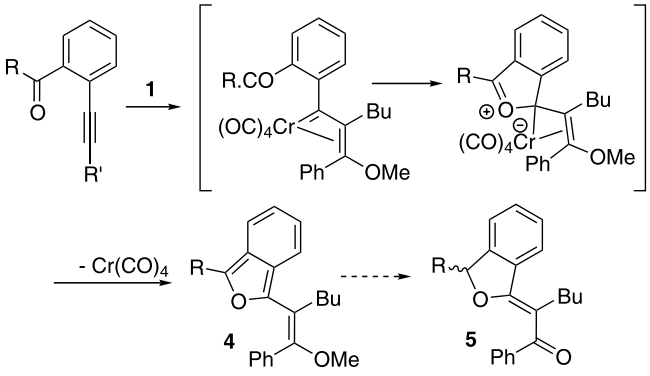
0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)00680-9

44% yield. A disubstituted acetylene was chosen so as to render the new aromatic ring in the hindered bi-aryl system **3** (Eq. (2)) di-*ortho* substituted. An oxidative work up employing Ce(IV)/0.1 M HNO_3 was employed in all reactions to avoid any regiochemical issues. It would be anticipated that an aryl–alkyl acetylene would ensure good regiochemical control to position the larger phenyl substituent adjacent to the hydroxyl function of the initially formed phenol.[10,17] In order to investigate possible steric and electronic effects exerted by the aryl group on the acetylene, *para*-substituted aromatic groups were screened in addition to the *ortho*-substituted aromatic acetylenes (Table 1). The benzannulations were conducted under dry state conditions[18] developed by Harrity and Kerr which were found to be generally superior to homogeneous methods. In our reactions the remainder of the mass balance, aside from starting material, was not accounted for as the reactions were screened only for quinone formation.

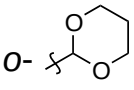
From Table 1 it would seem that an *ortho*-methyl or methoxy group gives good yields of benzannulated products **3a** to **3d**.[19] Carbonyl derivatives are unsatisfactory in the *ortho* position (**2e**,**g**,**i**,**l**) yielding mixtures of starting material and decomposition products. Herndon has used similar *o*-aldehyde/ketone aryl acetylenes to produce isobenzofuran intermediates via intramolecular cyclisation of chromium carbene species formed from treatment with Fischer carbene complexes.[20] By analogy, the failure of our substrates (**2e**,**g**,**i**,**l**) to undergo benzannulation could be due to a similar alternative cyclisation pathway, whereby the carbonyl compound eliminates chromium to give a benzofuran **4** (Scheme 1). This class of compounds is known[20,21] to be unstable and can decompose if tautomerisation to give the rearomatised product is not possible, as in our cases. The hydrolysed product **5**[20a] was not detected in the mixture of byproducts from our attempted benzannulations. It is surprising that the benzannulation of **2i** failed as a more hindered *o*-CO_2Me aryl acetylene has been successfully cyclised as part of a natural product synthesis.[22] This suggests subtle steric factors may have played a decisive role in that particular cyclisation.[23]

An *ortho*-formyl group protected as its 1,3-dioxane (**2k**) gave a moderate yield of the hydrolysed biaryl **3e** in 42% yield. Carbonyl derivatives in the *para* position (**2h**,**j**,**m**) gave moderate yields of biaryl **3**, but the *para*-



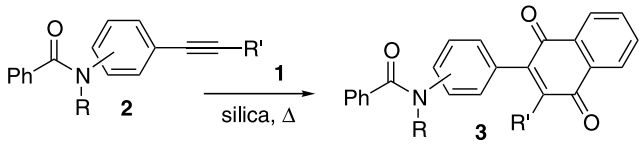
Scheme 1. Interception of reaction intermediates by *ortho*-carbonyl derivatives.

Table 1. Dötz benzannulations of aryl acetylenes **2**

Aryl acetylene	R	R′	*T* (°C)	*t* (h)	Yield (%)[a]
2a	*o*-Me	Ph	80	20	65
2b	*o*-OMe	Ph	80	20	57
2c	*o*-Me	^{n}Bu	100	2	64
2d	*o*-OMe	^{n}Bu	80	20	57
2e	*o*-CHO	^{n}Bu	100	2	0
2f	*p*-CHO	^{n}Bu	120	20	24
2g	*o*-COMe	^{n}Bu	120	12	0
2h	*p*-COMe	^{n}Bu	80	20	54
2i	*o*-CO_2Me	^{n}Bu	100	2	0
2j	*p*-CO_2Me	^{n}Bu	80	20	56
2k		^{n}Bu	100	2	42[b]
2l	*o*-CO·N^{i}Pr$_2$	Ph	80	12	0
2m	*o*-CO·N^{i}Pr$_2$	^{n}Bu	100	2	44
2n	*o*-NH_2	^{n}Bu	100	2	13[c,d]
2o	*p*-NH_2	^{n}Bu	100	2	38[d]
2p	*o*-NO_2	^{n}Bu	125	12	0
2q	*p*-NO_2	^{n}Bu	100	2	0
2r	*o*-Cl	^{n}Bu	100	2	79
2s	*p*-Cl	^{n}Bu	100	2	71

[a] Yield with respect to **1**. Standard conditions as in Ref. 17.
[b] Isolated yield of biaryl aldehyde derivative recovered after hydrolysis of acetal.
[c] Isolated as phenol due to decomposition with CAN.
[d] NMR yield from inseparable mixture of quinone and unidentified byproduct.

Table 2. Dötz benzannulations of anilides **2**



(3)

Aryl acetylene	R	R′	*T* (°C)	*t* (h)	Yield (%)
2t	*o*-NHCOPh	^{n}Bu	100	2	44
2u	*p*-NHCOPh	^{n}Bu	100	2	34
2v	*o*-NMeCOPh	^{n}Bu	100	2	50
2w	*p*-NMeCOPh	^{n}Bu	100	2	72
2x	*o*-N^{t}BuCOPh	^{n}Bu	100	2	0

formyl substrate (**2f**) was found to be sensitive to the reaction conditions and gave a poor yield of **3f**. The amino substituent in the *ortho* or *para* position (**2n**,**o**) gave poor yields of biaryl and the electron withdrawing nitro substituent (**2p**,**q**) gave no biaryl products at all. The chloro substituent gave excellent yields of biaryl whether in the *ortho* or *para* position.

To extend our survey we were interested in the amides of **2n** and **2o**. The benzanilides were easily prepared from the parent amines by stirring with benzoyl chloride in Et_2O to give **2t** and **2u** in 72 and 85% yields, respectively. Methylation with sodium metal and MeI in xylene gave the methyl anilides **2v** and **2w** in 55 and 58% yields, respectively. The *ortho*-^{t}butylanilide **2x** was prepared by the reverse procedure involving butylation of **2n** with $Cl_3C(C{=}NH)O^tBu$ and $BF_3{\cdot}OEt_2$ in hexane (83%) followed by benzoylation as before (62%). Under the standard dry state absorption conditions the protic anilides **2t** and **2u** underwent benzannulation with **1** in only moderate yields (Eq. (3), Table 2). The *ortho*-*N*-methyl anilide **2v** did not give a substantially higher yield on benzannulation, but the *para* derivative did. The more hindered ^{t}butyl analogue **2x** gave no reaction.

These results suggest that for the Dötz benzannulation of *ortho*-substituted aryl acetylenes it is essential that the functional group cannot interact with any reaction intermediates along the reaction pathway. In addition very electron withdrawing groups were found to be deleterious to the reaction. The *ortho* position is also sensitive to steric effects. We are currently looking at other benzannulation reactions of aryl acetylenes **2** so as to define the limitations of this strategy for biaryl synthesis.

Acknowledgements

We would like to thank the EPSRC and GlaxoSmith-Kline for financial support, Mr. T. Hollingworth and Mr. D. Hooper for providing mass spectra and Mr. T. J. Spencer for micro analytical data.

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23. We thank a referee for pointing this work out to us. In the light of this work (Ref. 22) we repeated the benzannulation of **2i** and under our reaction conditions detected no benzannulated products or hydrolysis products of type **5**.