## **Regioselectivity in Thermal Rhodium(II)-Catalysed Büchner-Type Reactions of Substituted Aryl Halides: Studies towards the Synthesis of Halide-Substituted Cycloheptatrienes**

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**Abstract:** The results of Büchner-type reactions of various substituted aryl halide derivatives with ethyl diazoacetate are presented, together with a discussion of factors affecting the regioselectivity of these processes.

Key words: Büchner reaction, regioselectivity, cycloaddition, carbenoids, rearrangement

The thermal or photochemical reaction of benzene with ethyl diazoacetate (1) to give a mixture of four cycloheptatrienyl ethyl ester derivatives 2-5 is commonly referred to as the Büchner reaction.<sup>1</sup> The development of a rhodium(II)-catalysed thermal Büchner process in 1980 allowed a significant reduction in the complexity of the product mixture, providing a synthetically useful method for the isolation of unconjugated cycloheptatrienyl esters **2** in high yields (Scheme 1).<sup>2</sup>



**Scheme 1** An example of a thermal or photochemical Büchner reaction. The current mechanistic interpretation of this process is that carbenoid formation followed by cycloaddition to the aromatic ring produces an unstable norcaradiene intermediate **6** which is in equilibrium with the more stable cycloheptatriene tautomer **2**. This is the kinetic product of the reaction. The other products are isomers of **2** formed by thermally or photochemically induced sigmatropic rearrangement.<sup>1</sup>

The Büchner reaction provides a convenient route to seven-membered carbocycles, both inter- and intramolecularly, and has found several applications in the synthesis of complex molecular targets.<sup>1,3</sup> The use of substituted ar-

SYNLETT 2011, No. 10, pp 1449–1453 Advanced online publication: 13.05.2011 DOI: 10.1055/s-0030-1260562; Art ID: D05511ST © Georg Thieme Verlag Stuttgart · New York omatic systems in Büchner-type reactions offers a potentially facile route towards functionalised cycloheptatriene systems and consequently has been the subject of continued interest in the literature.<sup>2,4</sup> However, such reactions have been associated with unpredictable, and often moderate levels of regioselectivity, which have curtailed their widespread use. In addition, previous reports on the use of aromatic halides in Büchner-type processes have generally been limited to the use of mono- or hexasubstituted derivatives.<sup>1,2,5</sup> During the course of our studies on the diversity-oriented synthesis (DOS) of the antibacterial agent emmacin, we became interested in exploiting the Büchner reaction of substituted aryl derivatives to generate novel molecular frameworks.<sup>6</sup> Herein we wish to report our findings on the regioselectivity observed in thermal rhodium(II)-catalysed Büchner-type reactions of various mono-, di-, and trisubstituted aromatic halides with ethyl diazoacetate (1). Attempts to probe the basis for this selectivity through variation of steric and electronic factors associated with the aromatic substrate are discussed. A mechanistic hypothesis which attempts to rationalise the observed product distributions is also presented.

Initially we sought to develop an efficient and general procedure for rhodium(II)-catalysed Büchner reactions involving ethyl diazoacetate (1). In principle, metal-catalysed Büchner-type reactions of substituted aromatic substrates may give rise to a number of different isomeric products as a result of cycloaddition of the metal carbenoid across chemically distinct  $\pi$  bonds of the aryl ring. Therefore our initial studies sought to avoid any regioselectivity complications through the use of 1,3,5-trifluorobenzene (7) as the aryl component, since only a single unconjugated cycloheptatriene 8 can be generated (as all  $\pi$  bonds are chemically equivalent). Adaptation of conditions previously reported by by Anciaux et al. for the Büchner reaction of various diazo esters and aryl substrates, which utilised rhodium(II) trifluoroacetate as the metal catalyst, proved optimal, providing 8 in a good isolated yield (Scheme 2).<sup>2</sup> Given this success, we were keen to investigate the application of these conditions in Büchner-type reactions of other substituted aryl halides, including those with the potential to yield two or more isomeric products. Towards this end, we turned our attention towards the use of various fluorine-substituted aromatic halides.



Scheme 2 Synthesis of 2,4,6-trifluorocycloheptatriene 8

Anciaux et al. have previously reported the rhodium(II) trifluoroacetate mediated reaction of methyl diazaoacetate (9) with fluorobenzene (10, Table 1).<sup>2a</sup> The reaction yielded an inseparable mixture of fluorocycloheptatrienes 11, 12, and 13 in a ratio of 80:12:8, which correspond to cycloaddition occurring across three different  $\pi$  bonds of the aromatic substrate (C<sub>3</sub>-C<sub>4</sub>, C<sub>2</sub>-C<sub>3</sub>, and C<sub>1</sub>-C<sub>2</sub>, respectively). Under similar conditions, the reaction of ethyl diazoacetate (1) in our hands yielded a comparable distribution of inseparable ethyl cycloheptatrienyl ester products 11–13 (Table 1).

Table 1Reaction of Methyl- and Ethyl Diazoacetate with Fluoro-<br/>benzene  $(10)^a$ 



<sup>a</sup> Reaction conditions: for **9**, 0.4 mol% catalyst, 22 °C; for **1**, 5 mol% catalyst, 0 °C. Overall yield refers to combined yield of all product isomers obtained.

<sup>b</sup> Relative product distribution obtained for the reaction of 1 determined by integration of characteristic signals present in the <sup>1</sup>H NMR spectra.

The use of 1,4-difluorobenzene (14) has the potential to yield two isomeric products; cycloaddition across the  $C_3$ - $C_4$  bond of the aromatic ring would give the symmetric 3,6-difluorocycloheptatriene 15 whereas cycloaddition across the  $C_2$ - $C_3$  bond would give the unsymmetrical 2,5-difluorocycloheptatriene 16 (Scheme 3). Pleasingly, only a single cycloheptatriene isomer 15 was observed in the reaction mixture.

The formation of substituted cycloheptatrienes was further investigated with a selection of 1,2-disubstituted ben-



Scheme 3 Reaction with 1,2-difluorobenzene (14) produced a single product isomer 15

zenes **17a–c** (Table 2). Such reactions have the potential to generate four possible isomers **18–21** corresponding to cycloaddition across the  $C_1$ – $C_2$ ,  $C_2$ – $C_3$ ,  $C_3$ – $C_4$ , or  $C_4$ – $C_5$  carbons of the aromatic ring (Table 2). With 1,2-difluorobenzene (**17a**) the reaction yielded an inseparable mixture of two isomers **20a** and **21a** in an overall yield of 68%; the major product was the symmetrical 4,5-difluorinated species **21a** with the 3,4-difluorinated compound **20a** generated as the secondary isomer. When the reaction was performed with 1,2-dichlorobenzene (**17b**) and 1,2-dibromobenzene (**17c**), a mixture of the corresponding halide-substituted cycloheptatrienyl ester products **20b,c** and **21b,c** was produced in a similar ratio to that obtained using 1,2-difluorobenzene. However, a small amount of isomer **19b,c** was also detected.

The regioselectivity of Büchner-type reactions using substituted aromatic systems has previously been rationalized on the basis of electronic factors; the rhodium-carbenoid species generated in situ is thought to be highly electrophilic and thus cyclaodditon is presumed to be favoured at more nucleophilic  $\pi$  bonds of the aromatic substrate.<sup>1b,2</sup> The results obtained in this study seem to be consistent with this line of reasoning. For example, in the case of 1,2disubsituted aromatic systems a simple explanation for the observed regioselectivity is that reaction becomes more favorable with increasing distance from the electronegative halogen atoms, thus a general preference for  $C_4$ - $C_5$  and  $C_3$ - $C_4$  addition products over  $C_1$ - $C_2$  and  $C_2$ - $C_3$ products as  $C_4$ - $C_5$  and  $C_3$ - $C_4 \pi$  bonds are expected to be more electron rich and therefore more nucleophilic. However, this explanation is somewhat simplistic and it is not immediately apparent how to apply such reasoning in other situations (e.g., the reaction of 1,4-disubsituted aromatics). Additional support for the dominance of electronic factors in general comes from a comparison of the product distributions obtained for the different 1,2-disubsituted systems investigated. Reactions with 1,2-dichlorobenzene (17b) and 1,2-dibromobenzene (17c) yielded a mixture of the corresponding halide-substituted cycloheptatrienyl ester products 20b,c and 21b,c in a similar ratio to that obtained using 1,2-difluorobenzene (17a, Table 2). The fact that the introduction of the more bulky bromine substituents had very little effect upon the distribution of isomers

**Table 2**Possible Isomeric Cycloheptatriene Products Resultingfrom the Reaction of Ethyl Diazoacetate with 1,2-Disubstituted ArylHaldies<sup>a</sup>



Dihalide	Overall yield (%) Relative product distribution (%)				
		18	19	20	21
17a	68	0	0	41	59
17b	69	0	10	37	53
17c	63	0	10	37	53

<sup>a</sup> Reaction conditions: 5 mol% catalyst, 0 °C. Overall yield refers to combined yield of all product isomers obtained. Relative product distributions determined by integration of characteristic signals present in the <sup>1</sup>H NMR spectra.

again suggests that the regioselectivity of the reaction is dominated by electronic rather than steric factors.

Though our results are consistent with the idea that the regioselectivity of Büchner-type processes involving substituted aromatics is dominated by electronic factors, the exact nature of, and mechanisms by which, such factors manifest themselves is poorly understood. Consequently a robust explanation for the observed product distributions when using different substituted aromatic systems has not been well characterized. Towards this end we were interested in examining reactions presented above in more depth in order to better delineate the basis of the observed regioselectivity.

Current mechanistic understanding suggests that Büchner-type reactions proceed by the cycloaddition of the rhodium-carbenoid species generated in situ (22) with the aromatic substrate 23 (Scheme 4).<sup>1,3a</sup> Preliminary computational modeling studies have indicated that this cycloaddition step is concerted but highly asynchronous.<sup>7</sup> The first 'event' (represented by 24 in Scheme 4) the development of a bonding interaction between one atom of the aryl ring and the carbenoid carbon to generate a transient cationic species of general form 25. In the second 'event' (26 in Scheme 4) a C–C bond is formed between an adjacent aryl ring carbon atom and the carbenoid carbon, thus



Scheme 4 Basic outline of postulated mechanism of Büchner-type reactions

furnishing an norcaradiene intermediate **27** which subsequently reacts on to produce products of the general form **28**.

Our preliminary modeling studies suggest that the ratedetermining step of the overall reaction sequence is the first 'event' of the cycloaddition process.<sup>7</sup> The second, smaller activation barrier is associated with the subsequent reactions of the aryl cation generated. On the basis of these observations we have developed a mechanistic hypothesis in an attempt to rationalise the outcome of the Büchner reactions presented above. The key assumption is that overall product distribution can presumably be related to the relative energy barriers associated with the two 'events' of the cycloaddition step.

As a representative case consider the reaction of 1,2-difluorobenzene (17a) with ethyl diazoacetate (1) discussed earlier. There are three chemically distinct sites at which the initial interaction between the aromatic ring and the carbenoid carbon could occur (C2, C3, and C4, boxes A, B, and C in Scheme 5) generating cations 29–31. In each case the intermediate cation can, in principle, then react by two possible pathways (steps d-i) to generate two different norcaradiene products; overall reaction at the three chemically distinct sites (boxes A, B, and C) leads to a total of four possible norcaradiene intermediates 32-35. Subsequent electrocyclic ring opening of each norcaradiene intermediate then furnishes the corresponding cycloheptatriene isomer. Overall, reaction at each of the chemically distinct aromatic carbon atoms can, in principle, generate two different cycloheptatriene products (Scheme 5). The whole reaction sequence can potentially yield four distinct cycloheptatriene products 18a-21a each corresponding to cycloaddition across the four chemically distinct  $\pi$  bonds of the substrate. The overall product distribution observed for the reaction of 17 can thus be rationalised as follows.



Scheme 5 Basic outline of our mechanistic hypothesis for the possible progress of the Büchner reaction of 1,2-difluorobezene (17a).

Firstly, the predominance of C3-C4 and C4-C5 addition products 20a and 21a is consistent with reaction at the C4 position (step c, box c) proceeding with a lower energy than reactions at the C2 (step a) and C3 (step b) positions. The slight preference for the C4–C5 addition product can then be explained if the subsequent reaction of **31** via step h proceeds with a lower activation barrier than reaction via step i. The absence of C1-C2 addition product 18a can also be accounted for. If one assumes that the energy barrier to reaction at the C2 position (step a) is too high relative to that associated with reaction at the C3 or C4 positions (steps b and c, respectively) for there to be any substantial reactivity via the pathways outlined in box A, then one would not expect any of the C1-C2 addition product 18a to be formed (as it is believed that this compound can only arise via initial reaction at the C2 position).

In conclusion we have reported the results of thermal rhodium(II)-catalysed Büchner-type reactions of various substituted aryl halide derivatives with ethyl diazoacetate. The isomeric ratios of the substituted cycloheptatriene products obtained are consistent with the generally accepted theory that the regioselectivity of Büchner-type processes is dominated by electronic factors associated with the highly electrophilic rhodium-carbenoid species.

A tentative mechanistic hypothesis has been proposed which attempts to more fully delineate the progress of these reactions and thus better rationalise the basis of the observed regioselectivity. Such information may prove valuable in terms of more accurately predicting, a priori, the regioselectivity of Büchner-type reactions of substituted aromatic components, which may facilitate the application of such processes in a wider synthetic context.

## Sample Experimental Protocol: Ethyl 2,4,6-Trifluorocyclohepta-2,4,6-trienecarboxylate (8)

To a solution of  $Rh_2(O_2CCF_3)_4$  (29.0 mg, 5 mol%) in 1,3,5-trifluorobenzene (5.8 mL, 43.8 mmol, 50 equiv) at 0 °C was added dropwise ethyl diazoacetate (200 mg, 0.876 mmol, 1 equiv) in a controlled manner over 30 min. The solution was stirred for a further 1 h, and the solvent was then removed under reduced pressure. The crude material was purified by flash column chromatography to give the desired compound **8** as a colourless oil (157 mg, 0.721 mmol, 85%).

 $R_f = 0.23$  (SiO<sub>2</sub>; 15:1 hexane–EtOAc). IR (neat): 1742 (s, ester), 1663 (s), 1597 (w, C=C), 1127 (s, CO), 1090 (s, CF) cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 6.09-5.97$  [2 H, m, C(=O)CHCHCFCH and C(=O)CHCFCH], 5.30 [1 H, dd, J = 13.5, 9.5 Hz, C(=O)CHCH], 4.24–4.15 (2 H, m, CH<sub>2</sub>CH<sub>3</sub>), 3.83 [1 H, dd, J = 19.5, 9.5 Hz, C(=O)CH], 1.26 (3 H, t, J = 7.0 Hz, CH<sub>2</sub>CH<sub>3</sub>]. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 167.38$  [C(=O)], 160.55–157.91 [dd, J = 249.0, 16.0

Hz, C(=O)CHCFCHCF], 159.30–156.75 [dd, J = 240.5, 16.0 Hz, C(=O)CHCHCF], 158.05–155.04 [dd, J = 290.0, 15.5 Hz, C(=O)CHCF], 102.89 [ddd, J = 39.5, 31.0, 4.5 Hz, C(=O)CHCH-CFCH], 101.68 [dd, J = 40.0, 28.5 Hz, C(=O)CHCFCH], 96.92 [app dt, J = 32.5, 5.0 Hz, C(=O)CHCH], 62.11 (CH<sub>2</sub>), 42.62 [dd, J = 27.5, 9.5 Hz, C(=O)CH], 14.00 (CH<sub>3</sub>).

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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## **References and Notes**

- (a) Doyle, M. P.; McKervey, M. A.; Ye, T. Modern Catalytic Methods for Organic Synthesis with Diazo Compounds; Wiley-Interscience: New York, **1998**. (b) Ye, T.; McKervey, M. A. Chem. Rev. **1994**, *94*, 1091.
- (2) (a) Anciaux, A. J.; Demonceau, A.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssie, P. J. Chem. Soc., Chem. Commun. 1980, 16, 765. (b) Anciaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A. J.; Warin, R.; Teyssie, P. J. Org. Chem. 1981, 46, 873.
- (3) (a) Kürtz, L.; Czakó, B. Strategic Applications of Named Reactions in Organic Synthesis; Elsevier Academic Press: Amsterdam, 2005. (b) Maguire, A. R.; Buckley, N. R.; O'Leary, P.; Ferguson, G. J. Chem. Soc., Perkin Trans. 1

**1998**, *24*, 4077. (c) Maguire, A. R.; Buckley, N. R.; O'Leary, P.; Ferguson, G. *Chem. Commun.* **1996**, *22*, 2595. (d) Kane, J. L.; Shea, K. M.; Crombie, A. L.; Danheiser, R. L. *Org. Lett.* **2001**, *3*, 1081. (e) Frey, B.; Wells, A. P.; Rogers, D. H.; Mander, L. N. *J. Am. Chem. Soc.* **1998**, *120*, 1914.

- (4) See ref. 2a and 2b. See also: (a) Lovely, C. J.; Browning, R. G.; Badarinarayana, V.; Dias, H. V. R. *Tetrahedron Lett.*2005, 46, 2453. (b) Morilla, M. E.; Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Perez, P. J. Organometallics 2004, 23, 293.
- (5) See ref. 1a, 2a, and 2b. See also: Gale, D. M. J. Org. Chem. 1968, 33, 2536.
- (6) For the discovery of the antibacterial agent emmacin, see:
  (a) Wyatt, E. E.; Fergus, S.; Galloway, W. R. J. D.; Bender, A.; Fox, D. J.; Plowright, A. T.; Jessiman, A. S.; Welch, M.; Spring, D. R. *Chem. Commun.* 2006, 3296. (b) Wyatt, E. E.; Fergus, S.; Galloway, W. R. J. D.; Bender, A.; Thomas, G. L.; Welch, M.; Loiseleur, O.; Plowright, A. T.; Spring, D. R. *Chem. Commun.* 2008, 4962. For recent reviews on DOS, see: (c) Schreiber, S. L. *Nature (London)* 2009, 457, 153. (d) Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R. *Nat. Commun.* 2010, *1*, 80. (e) Nielsen, E.; Schreiber, S. L. *Angew. Chem. Int. Ed.* 2008, 47, 48. (f) Galloway, W. R. J. D.; Bender, A.; Welch, M.; Spring, D. R. *Chem. Commun.* 2009, 2446. (g) Cordier, C.; Morton, D.; Murrison, S.; Nelson, A.; O'Leary-Steele, C. *Nat. Prod. Rep.* 2008, *25*, 719.
- (7) A full account of our computational modelling studies on the Büchner reactions described in this paper will be reported in due course.