Palladium-catalysed synthesis of 1-isoindolecarboxylic acid esters and sequential Diels–Alder reactions: access to bridged- and fused-ring heterocycles†

Daniel Solé* and Olga Serrano

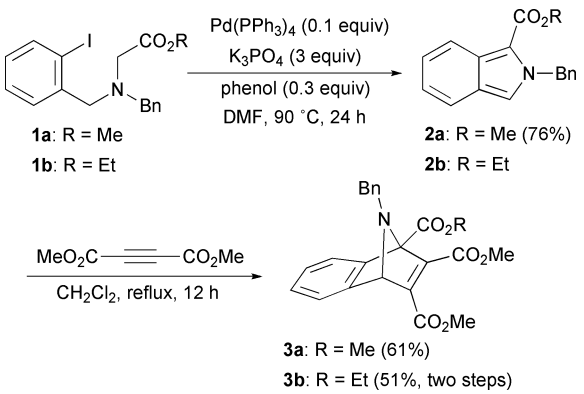
Received 18th May 2009, Accepted 2nd July 2009
First published as an Advance Article on the web 9th July 2009
DOI: 10.1039/b909701e

The Pd-catalysed intramolecular α-arylation of α-amino acid esters provides a useful methodology for the synthesis of substituted isoindole derivatives, which have been used in Diels–Alder reactions to access diverse skeletal frameworks.

Isoindoles have long attracted the attention of organic chemists due to their high level of reactivity in cycloaddition reactions[1,2] and fluorescent and electroluminescent properties.[3] However, the difficulties in the preparation of isoindoles together with their instability have frequently restricted their synthetic use, creating a demand for new and straightforward methods to access these substrates. In this context, recent progress in synthetic organic chemistry has led to the development of new methods for the preparation of diversely substituted isoindoles.[4]

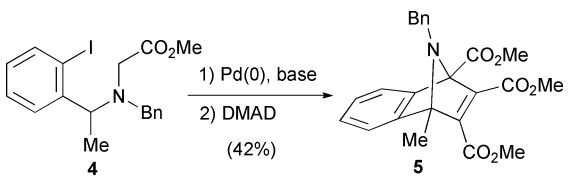
As part of our ongoing program on the synthesis of nitrogen heterocycles, we have recently reported an efficient methodology for the synthesis of indoles based on the Pd(0)-catalysed intramolecular α-arylation of β-(2-iodoanilino) esters.[5] Continuing our research on this palladium chemistry,[6] we considered that the intramolecular coupling of aryl halides and ester enolates might also be a suitable route towards substituted isoindoles. The ester group was an attractive substituent not only because it could be elaborated into other frameworks, but also because, as part of a conjugated donor–acceptor system with the nitrogen, it would provide the isoindole nucleus with some electronic stabilisation. In this communication we present our preliminary studies on the application of the Pd(0)-catalysed arylation reaction to the synthesis of 1-isoindolecarboxylic acid esters[7] to be used in Diels–Alder reactions (Scheme 1).

Our standard conditions developed for the synthesis of 3-indolecarboxylic acid esters employ the catalyst $Pd(PPh_3)_4$ and the base K_3PO_4 in the presence of a catalytic quantity of phenol in DMF.[5] When the same conditions were applied to the reaction of α-amino ester **1a**, a clean reaction mixture was obtained, from which 1-isoindolecarboxylic acid ester **2a**, resulting from the Pd catalysed dehydrogenation[8] of the initially formed α-arylation compound,[9] was isolated in 76% yield (Scheme 1). However, isoindole **2a** was difficult to characterise because of its high tendency to undergo aerial oxidation on standing in solution. Nevertheless, to our delight, treatment of **2a** with dimethyl acetylenedicarboxylate in dichloromethane at reflux afforded cycloadduct **3a** in 61% yield.



Scheme 1 Sequential Pd(0)-catalysed α-arylation and Diels–Alder reaction of amino esters **1a**,**b**.

The α-arylation/dehydrogenation/Diels–Alder reaction sequence was also successfully applied with α-aminoesters **1b** and **4**, although due to their instability, the isoindole intermediates were not purified and the crude arylation reaction mixtures were directly treated with DMAD in order to characterise the Diels–Alder cycloadducts (Schemes 1 and 2). It should be noted that cycloadducts **3a-b** and **5** are robust compounds, which allowed the NMR spectra to be recorded in $CDCl_3$ at 50 °C, thus overcoming conformational mobility problems. In contrast with this stability, a closely related cycloadduct resulting from the Diels–Alder reaction of a 1-isoindolecarboxamide with DMAD displays a high tendency to undergo the retro-process.[4a]



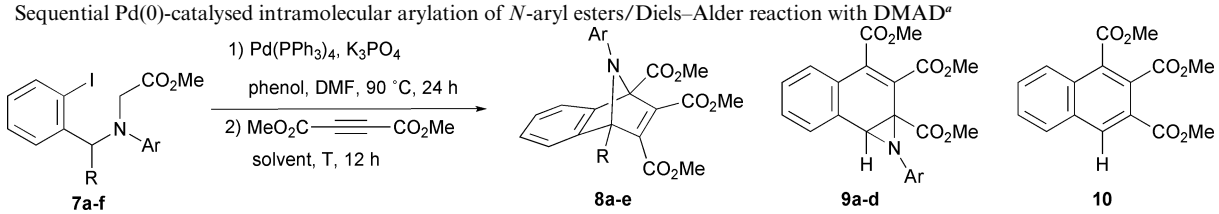
Scheme 2 Sequential Pd(0)-catalysed α-arylation and Diels–Alder reaction of amino ester **4**.

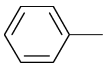
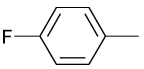
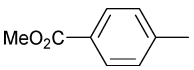
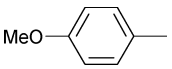
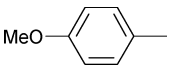
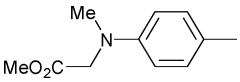
The Diels–Alder reactions of isoindole **2a** with other dienophiles were also examined. Thus, for example, treatment of crude **2a** with NMM afforded a 1:2 mixture of the starting material and the ENDO cycloadduct **6**;[10] however, further separation and characterisation of **6** failed because of partial decomposition by retro-reaction during NMR experiments (Scheme 3).

Laboratori de Química Orgànica, Facultat de Farmàcia, and Institut de Biomedicina (IBUB), Universitat de Barcelona, Av., Joan XXIII s/n, 08028, Barcelona, Spain. E-mail: dsole@ub.edu; Fax: +34 93 402 45 39; Tel: +34 93 402 45 40

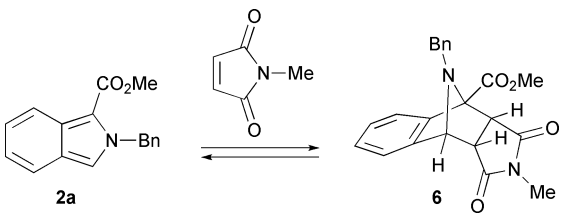
† Electronic supplementary information (ESI) available: Experimental procedure and characterisation data for new compounds. See DOI: 10.1039/b909701e

Table 1 Sequential Pd(0)-catalysed intramolecular arylation of *N*-aryl esters/Diels–Alder reaction with DMAD[a]



Entry		Ar	R	Solvent	T		Products (yield)[b]
1	**7a**		H	CH_2Cl_2	reflux	**8a** (62%)	
2	**7a**			DMF	90 °C	**8a** (20%)	**9a** (23%)
3	**7b**		H	CH_2Cl_2	reflux	**8b** (46%)	
4	**7b**			DMF	90 °C	**8b** (10%)	**9b** (35%)
5	**7c**		H	CH_2Cl_2	reflux	**8c** (46%)	
6	**7d**		H	CH_2Cl_2	reflux	**8d** (37%)	**9d** (23%)
7	**7e**		Me	CH_2Cl_2	reflux	**8e** (50%)	
8	**7e**			DMF	90 °C	**8e** (42%)	
9	**7f**		H	CH_2Cl_2	reflux		**10** (55%)

[a] α-Arylation reactions were performed using **7** (0.2 mmol), $Pd(PPh_3)_4$ (10 mol%), K_3PO_4 (3 equiv) and phenol (30 mol%) in DMF (3 mL) at 90 °C for 24 h. Diels–Alder reactions were performed using the crude isoindoles and DMAD (1.5 equiv) in CH_2Cl_2 (10 mL) at reflux or in DMF (5 mL) at 90 °C for 12 h. [b] Isolated yield.



Scheme 3 Diels–Alder reaction of isoindole **2a** with NMM.

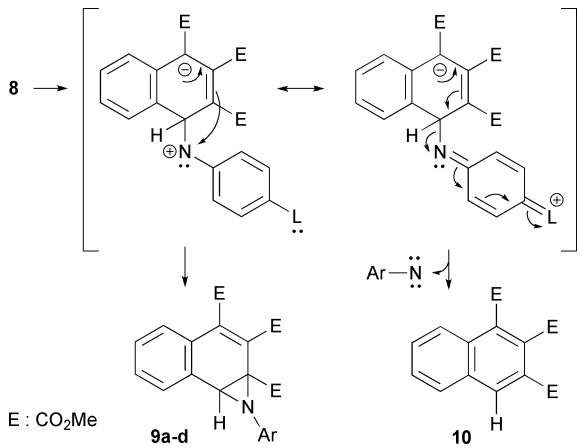
On the other hand, no cycloadduct could be obtained in the reactions of **2a** with methyl propiolate, maleic anhydride or *p*-benzoquinone, the isoindole being recovered unchanged.

The studies on the α-arylation/Diels–Alder sequence were extended to amino esters **7a-f**, which bear aryl substituents at the nitrogen. Interestingly, somewhat different behaviour was observed with these substrates. Thus, while **7a**, **7b**, and **7c** afforded the cycloadducts **8a**, **8b**, and **8c**, respectively, as the only isolated products (Table 1, entries 1, 3, and 5),[11] **7d** gave cycloadduct **8d** (37%) and aziridine **9d** (23%) under the same reaction conditions (Table 1, entry 6). The analysis of the crude reaction mixture showed a 4:1 ratio of **8d** and **9d**, suggesting a partial transformation of the cycloadduct into the aziridine during the purification process. In fact, on standing in chloroform solution at room temperature, **8d** slowly evolved into **9d**, the conversion being completed after a lengthy heating at reflux. Interestingly, when starting from **7a** and **7b** and using DMF as the solvent in the Diels–Alder step, aziridines **9a** and **9b** were obtained, respectively, as the main products (Table 1, entries 2 and 4). However, under these reactions conditions **7c** afforded a complex mixture in which the only identifiable products were those resulting from the aerobic oxidation of the isoindole. When starting from amino ester **7e**, cycloadduct **8e** was obtained regardless of whether the solvent in the cycloaddition reaction was CH_2Cl_2 or DMF (Table 1, entries 7 and 8).

Finally, the α-arylation/Diels–Alder sequence was attempted with amino ester **7f**. However, in this case, neither the Diels–Alder cycloadduct nor aziridine were detected in the reaction mixture, which contained trimethyl naphthalenetricarboxylate (**10**, 55% yield)[12] as the major and only identifiable product (Table 1, entry 9).

It is known that the Diels–Alder cycloadducts of isoindoles undergo transformation into other systems,[4b] but, to the best of our knowledge, their evolution into aziridines has not been previously described. Similarly, the formation of aromatic systems (*i.e.* naphthalenes) by nitrene extrusion from the azanorbornenes produced in the Diels–Alder reaction of pyrroles and isoindoles is a common reaction when the nitrogen contains an amino group,[4b,13]

but there is no reported precedent in N-aryl systems. Both novel processes are somewhat surprising, particularly because similar reactions were not observed from cycloadducts **3a-b** and **5**, which bear a benzyl group at the nitrogen (vide supra). This stability, together with the markedly faster evolution of the cycloadduct intermediates bearing electron-donating groups at the aryl substituent, suggested that both unexpected transformations could be explained by the participation of a nitrenium intermediate. Thus, the heterolysis of the cycloadduct would give a zwitterionic intermediate, stabilised by resonance,[14] which in turn would undergo intramolecular nucleophilic attack to afford the corresponding aziridine (Scheme 4). The formation of aziridines as the main products in the Diels–Alder reactions in DMF may reflect not only an increase in temperature but also solvent polarity. On the other hand, naphthalene **10** would be formed by nitrene extrusion from the corresponding zwitterionic intermediate.



Scheme 4 Proposed mechanisms for the formation of **9a-d** and **10**.

In summary, in this report we show that the Pd(0)-catalysed intramolecular arylation of α-amino acid esters and a sequential Diels–Alder reaction offer a new opportunity to create complex and diverse scaffolds from readily accessible starting materials. Further investigations on the scope and synthetic applications of this sequence are currently in progress and will be reported in due course.

Acknowledgements

We thank the "Ministerio de Educación y Ciencia", Spain, for financial support (project CTQ2006-00500/BQU).

Notes and references

1 (*a*) R. J. Sundberg, *Comprehensive Heterocyclic Chemistry II*, Vol. 2, A. R. Katritzky, C. W. Rees, E. F. V. Scriven, Eds., Pergamon, Oxford, 1996, Chap. 3, 119; (*b*) T. J. Donohoe, Product class 14: 1H- and 2H-isoindoles, *Sci. Synth.*, 2001, **10**, 653.

2 For recent examples, see: (*a*) Y.-L. Chen, M.-H. Lee, W.-Y. Wong and A. W. M. Lee, *Synlett*, 2006, 2510; (*b*) Z. Chen, P. Müller and T. M. Swager, *Org. Lett.*, 2006, **8**, 273; (*c*) R. Rincón and J. Plumet, *Synlett*, 2008, 911.

3 See for example: B.-X. Mi, P.-F. Wang, M.-W. Liu, H.-L. Kwong, N.-B. Wong, C.-S. Lee and S.-T. Lee, *Chem. Mater.*, 2003, **15**, 3148.

4 (*a*) D. Kadzimirsz, D. Hildebrandt, K. Merz and G. Dyker, *Chem. Commun.*, 2006, 661; (*b*) S. Duan, D. K. Sinha-Mahapatra and J. W. Herndorn, *Org. Lett.*, 2008, **10**, 1541; (*c*) B. W.-Q. Hui and S. Chiba, *Org. Lett.*, 2009, **11**, 729.

5 D. Solé and O. Serrano, *J. Org. Chem.*, 2008, **73**, 2476.

6 (*a*) D. Solé, L. Vallverdú and J. Bonjoch, *Adv. Synth. Catal.*, 2001, **343**, 439; (*b*) D. Solé, L. Vallverdú, E. Peidró and J. Bonjoch, *Chem. Commun.*, 2001, 1888; (*c*) D. Solé, L. Vallverdú, X. Solans, M. Font-Bardia and J. Bonjoch, *J. Am. Chem. Soc.*, 2003, **125**, 1587; (*d*) D. Solé, X. Urbaneja and J. Bonjoch, *Tetrahedron Lett.*, 2004, **45**, 3131; (*e*) D. Solé and O. Serrano, *J. Org. Chem.*, 2008, **73**, 9372.

7 (*a*) G. Cignarella, F. Savelli and P. Sanna, *Synthesis*, 1975, 252; (*b*) G. Cignarella, R. Cerri, G. Grella and P. Sanna, *Gazz. Chim. Ital.*, 1976, **106**, 65.

8 For a related process, see: R. Grigg, A. Somasunderam, V. Sridharan and A. Kepp, *Synlett*, 2008, 97.

9 O. Gaertzen and S. L. Buchwald, *J. Org. Chem.*, 2002, **67**, 465.

10 R. P. Kreher, G. Sewarte-Ross and G. Vogt, *Chem. Ber.*, 1992, **125**, 183.

11 A. R. Katritzky, M. H. Paluchowska and J. K. Gallos, *J. Heterocycl. Chem.*, 1989, **26**, 421.

12 The structure of **10** was unambiguously established from its ^{1}H and ^{13}C NMR data, with the aid of 2D-NMR experiments (HSQC and HMBC). These data are consistent with those described for other 1,2,3-trisubstituted naphthalenes,[4b] but clearly differ from those previously reported for **10**; see: M. A. Bennett and E. Wenger, *Organometallics*, 1996, **15**, 5536.

13 H. Hart, C.-Y. Lai, G. Chukuemeka-Nwokogu and S. Shamouilian, *Tetrahedron*, 1987, **43**, 5203.

14 L. Greci, R. Castagna, P. Carloni, P. Stipa, C. Rizzoli, L. Righi and P. Sgarabotto, *Org. Biomol. Chem.*, 2003, **1**, 3768.