CHEMCOMM Communication
www.rsc.org/chemcomm

Palladium-catalysed intramolecular annulation of 2-haloanilines and ketones: enolate arylation *vs.* nucleophilic addition to the carbonyl group†

Daniel Solé,* Lluís Vallverdú, Emma Peidró and Josep Bonjoch*

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028-Barcelona, Spain. E-mail: bonjoch@farmacia.far.ub.es; dsole@farmacia.far.ub.es; Fax: +34 93 402 18 96; Tel: +34 93 402 45 40

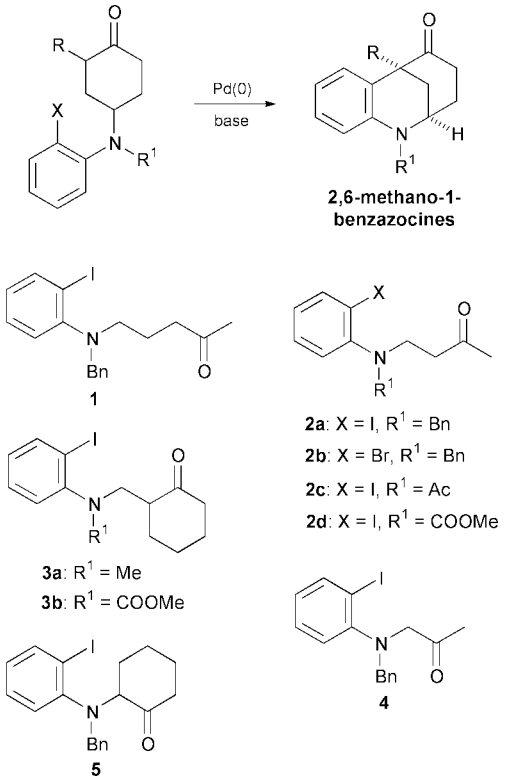
Received (in Cambridge, UK) 28th June 2001, Accepted 6th August 2001
First published as an Advance Article on the web 3rd September 2001

Two alternative annulation pathways involving either the enolate arylation or the addition to the ketone carbonyl group can operate in the Pd-catalysed intramolecular coupling of 2-haloanilines and ketones.

During the recent years there has been a growing interest in the palladium-catalysed coupling reactions of aryl[1–4] and vinyl[5] halides and enolates. Perhaps the most extensive study has been done on the palladium-catalysed intermolecular coupling of aryl halides and ketone enolates, while, in contrast, the intramolecular version of the reaction has received less attention.

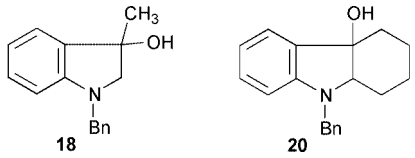
In this context, we have recently reported that the palladium-catalysed intramolecular coupling of 2-haloanilines and ketone enolates provides a useful synthetic approach to the hexahydro-2,6-methano-1-benzazocine ring system.[3d]

Continuing our palladium chemistry studies we decided to extend the carbocyclisation process to the construction of other nitrogen heterocycles by varying the relative position of the 2-haloaniline moiety and the ketone carbonyl group. Three types of starting ketones were studied: γ-(2-iodoanilino) ketone **1**, β-(2-haloanilino) ketones **2a–2d**, **3a** and **3b**, and α-(2-iodoanilino) ketones **4** and **5**.‡



† Dedicated with great appreciation to Professor Francisco Camps for his contribution to organic chemistry.

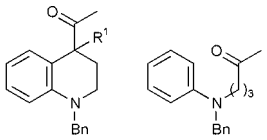
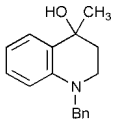
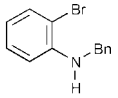
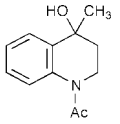
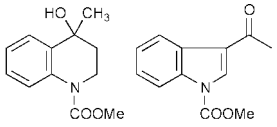
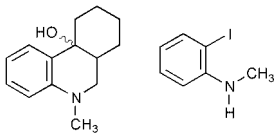
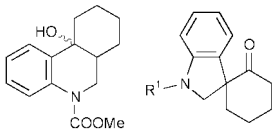
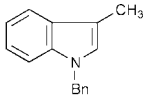
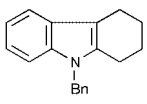
We examined the intramolecular coupling of these substrates under similar conditions to those we used for the synthesis of 2,6-methano-1-benzazocines: method A, 0.2 equiv. of $Pd(PPh_3)_4$ and 3 equiv. of KO*t*-Bu in THF at reflux; method B, 0.2 equiv. of $PdCl_2(PPh_3)_2$ and 3 equiv. of Cs_2CO_3 in THF in a sealed tube at 110 °C.[3d] When the above (2-haloanilino) ketones were submitted to the cyclisation conditions of method A, no cyclisation product was obtained, and only compounds arising from hydrodehalogenation and degradation of the amino ketone moiety were isolated. In contrast, we found that using method B led to two different and competitive cyclisation pathways,[6] namely enolate arylation and nucleophilic addition to the carbonyl group, depending on the structure of the starting amino ketone. The results are summarised in Table 1. Thus, Pd-catalysed intramolecular coupling of γ-(2-iodoanilino) ketone **1** in the presence of $PdCl_2(PPh_3)_2$ and Cs_2CO_3 in THF at 110 °C (entry 1) took place exclusively at the α-position to give quinolines **6** and **7**, although in low yield, together with the hydrodehalogenation compound **8**. The alcohol **7** is probably formed by oxidation of **6** under the reaction conditions; in fact, longer reaction times resulted in the formation of **7** as the major cyclisation product. However, under essentially the same reaction conditions, both β-(2-haloanilino) ketones **2a–2d**, and **3a** and **3b**, and α-(2-haloanilino) ketones **4** and **5** afforded as the main product compounds resulting from the addition of the arylpalladium intermediate to the carbonyl group. It is noteworthy that the intramolecular nucleophilic addition of arylpalladium halides to ketones is an uncommon transformation that has not been described until very recently.[7,8] After the initial results in the aforementioned palladium-catalysed processes, we worked to optimise conditions to promote the nucleophilic addition to the carbonyl group. Both the addition of triethylamine and the use of toluene as the solvent, instead of THF, increased the yield of the annulation reactions (entry 3 *vs.* 2, 8 *vs.* 7 and 12 *vs.* 11).[9] Some additional points can be mentioned. The use of bromide **2b**, instead of iodide **2a**, decreased the yield of cyclisation and resulted mainly in the formation of the degradation compound **10** (entry 4 *vs.* 3). Interestingly, in the β-amino ketone series changing the substituent at the nitrogen atom from alkyl to methoxycarbonyl resulted in the formation of significant amounts of the product from arylation of the ketone enolate (entry 6 *vs.* 3, 9 *vs.* 7, and 10 *vs.* 8). Finally, the Pd-catalysed cyclisation of α-(2-iodoanilino) ketones **4** and **5** (entries 11–14) exclusively afforded **18** and **20**, respectively, from the addition to the carbonyl group, as



was confirmed by careful analysis of the reaction mixtures. Nevertheless, these compounds could not be characterised due

 DOI: 10.1039/b105686g

Table 1 Pd(0)-catalysed intramolecular annulation of (2-haloanilino) ketones **1**–**5**[a]

Entry	Substrate	Solvent	Additive (equiv.)	Products (yield)[b]
1	**1**	THF[c]	—	 **6** R^1 = H (20%) **7** R^1 = OH (9%) **8** (25%)
2	**2a**	THF[c]	—	 **9** (40%)
3	**2a**	Toluene[d]	Et_3N (2)	**9** (45%)
4	**2b**	Toluene[d]	Et_3N (2)	 **9** (15%) **10** (46%)
5	**2c**	Toluene[d]	Et_3N (2)	 **11** (65%)
6	**2d**	Toluene[d]	Et_3N (2)	 **12** (44%) **13** (29%)
7	**3a**	THF[c]	Et_3N (10)	 **14** (65%, 3.5:1) **15** (30%)
8	**3a**	Toluene[c]	Et_3N (10)	**14** (73%, 3.5 : 1)
9	**3b**	THF[c]	Et_3N (10)	 **16** (32%, 2:1) **17** R^1 = COOMe (24%)
10	**3b**	Toluene[c]	Et_3N (10)	**16** (45%, 2 : 1) **17** (31%)
11	**4**	THF[e]	Et_3N (10)[f]	 **19** (66%)
12	**4**	Toluene[d]	Et_3N (10)[f]	**19** (83%)
13	**5**	THF[e]	Et_3N (10)[f]	 **21** (86%)
14	**5**	Toluene[d]	Et_3N (10)[f]	**21** (87%)

[a] Method B: $PdCl_2(PPh_3)_2$ (0.2 equiv.) and Cs_2CO_3 (3 equiv.) in a sealed tube at 110 °C. [b] Yields refer to pure isolated products. [c] 48 h. [d] 24 h. [e] 65 h. [f] After the cyclisation reaction the crude mixture was treated with TFA.

to their instability and were converted to the corresponding indoles **19** and **21** by treatment with TFA.

In summary, we have reported that two alternative pathways can operate in the Pd-catalysed intramolecular coupling of 2-haloanilines and ketones. At this point, it is not clear why one reaction or the other is preferred or what the chemoselectivity control elements are. However, the results obtained when changing the substituent at the nitrogen atom from alkyl to methoxycarbonyl seem to indicate that the regioselectivity of the enolate formation[10] could be the origin of the change in the annulation pathway. Further studies to clarify this point are underway in our laboratory.

Notes and references

‡ Satisfactory analytical (combustion and/or high resolution mass) and spectral (^1H and ^{13}C NMR) data were obtained for all new compounds.

1 For the Pd-catalysed intermolecular coupling of aryl halides and enolates, see: M. Kawatsura and J. F. Hartwig, *J. Am. Chem. Soc*., 1999, **121**, 1473; J. M. Fox, X. Huang, A. Chieffi and S. L. Buchwald, *J. Am. Chem. Soc*., 2000, **122**, 1360; D. A. Culkin and J. F. Hartwig, *J. Am. Chem. Soc*., 2001, **123**, 5816; and references therein.

2 For the Pd-catalysed intramolecular coupling of aryl halides and stabilized enolates, see: M. A. Ciufolini, H.-B. Qi and M. E. Browne, *J. Org. Chem*., 1988, **53**, 4149.

3 (*a*) For the Pd-catalysed intramolecular coupling of aryl halides and ketone and aldehyde enolates, see: H. Muratake, A. Hayakawa and N. Natsume, *Tetrahedron Lett*., 1997, **38**, 7577; (*b*) H. Muratake and N. Natsume, *Tetrahedron Lett*., 1997, **38**, 7581; (*c*) H. Muratake and H. Nakai, *Tetrahedron Lett*., 1999, **40**, 2355; (*d*) D. Solé, L. Vallverdú and J. Bonjoch, *Adv. Synth. Catal*., 2001, **343**, 439.

4 For the Pd-catalysed intramolecular coupling of aryl halides and amide enolates, see: K. H. Shaughnessy, B. C. Hamann and J. F. Hartwig, *J. Org. Chem*., 1998, **63**, 6546; R. Freund and W. W. K. R. Mederski, *Helv. Chim. Acta*, 2000, **83**, 1247; T. Honda, H. Namiki and F. Satoh, *Org. Lett*., 2001, **3**, 631; S. Lee and J. F. Hartwig, *J. Org. Chem*., 2001, **66**, 3402.

5 E. Piers and J. Renaud, *J. Org. Chem*., 1993, **58**, 11; T. Wang and J. M. Cook, *Org. Lett*., 2000, **2**, 2057; X. Liu, T. Wang, Q. Xu, C. Ma and J. M. Cook, *Tetrahedron Lett*., 2000, **41**, 6299; D. Solé, E. Peidró and J. Bonjoch, *Org. Lett*., 2000, **2**, 2225; A. Chieffi, K. Kamikawa, J. Ahman, J. M. Fox and S. L. Buchwald, *Org. Lett*., 2001, **3**, 1897.

6 Recently, a third reaction pathway, involving a palladium-catalysed redox process to form enones from α-(2-bromobenzyl) ketones under reaction conditions similar to those reported in this work, has been described: K. Högenauer and J. Mulzer, *Org. Lett*., 2001, **3**, 1495. However, this reaction has never been observed with any of the 2-haloanilino ketones studied in this work.

7 L. G. Quan, M. Lamrani and Y. Yamamoto, *J. Am. Chem. Soc*., 2000, **122**, 4827.

8 For the intramolecular addition of vinylpalladium intermediates to ketones,[8a] aldehydes[8b] and nitriles,[8c] see: (*a*) L. G. Quan, V. Gevorgyan and Y. Yamamoto, *J. Am. Chem. Soc*., 1999, **121**, 3545; (*b*) R. C. Larock, M. J. Doty and S. Cacchi, *J. Org. Chem*., 1993, **58**, 4579; V. Gevorgyan, L. G. Quan and Y. Yamamoto, *Tetrahedron Lett*., 1999, **40**, 4089; (*c*) R. C. Larock, Q. Tian and A. A. Pletnev, *J. Am. Chem. Soc*., 1999, **121**, 3238.

9 Indole **13** (see entry 6 Table 1) arises from the oxidation, under the reaction conditions, of the 3-acetylindoline initially formed by α-arylation.

10 The effects of α- and β-heteroatom-containing groups on the regioselectivity of enolate formation are well known: V. A. Martin, D. H. Murray, N. E. Pratt, Y. Zhao and K. F. Albizati, *J. Am. Chem. Soc*., 1990, **112**, 6965; ; Moreover, the introduction of electron-withdrawing groups on the nitrogen atom of amino ketones increases the tendency for enolization toward nitrogen: M. E. Garst, J. N. Bonfiglio, D. A. Grudoski and J. Marks, *J. Org. Chem*., 1980, **45**, 2307.