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Synthesis of benzocyclic ketones via palladium-catalyzed cyclization of ω-(2-iodoaryl)alkanenitriles

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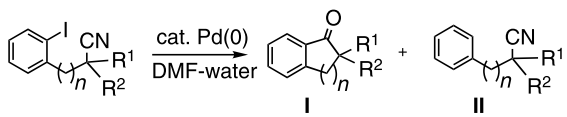
Abstract—An efficient procedure for the synthesis of 2,2-disubstituted benzocyclic ketones by intramolecular carbopalladation of nitriles has been developed. The cyclization of substituted 3-(2-iodoaryl)propanenitriles affords indanones in high yields. The reaction is compatible with a wide variety of functional groups. This chemistry has been extended to the synthesis of tetralones, a 9-fluorenone and a cyclopentenone. © 2002 Elsevier Science Ltd. All rights reserved.

Benzocyclic ketones are versatile and useful synthetic intermediates in the agrochemical and pharmaceutical industries.[1] 1-Indanone derivatives exhibit useful biological activity (e.g. antihypertensive or bronchodilatory)[1a,2] and also serve as important building blocks in the synthesis of many natural products[3] and medicinal substances.[4] α-Tetralones represent a valuable class of starting materials and intermediates for the synthesis of biologically active lignans,[5] cytotoxic antileukemic alkaloids,[6] and other pharmaceutical preparations.[1d,7] Classical means for the synthesis of benzocyclic ketones include intramolecular Friedel–Crafts acylation,[6a,8] Vilsmeier–Haack cyclization,[1c] and variations of carbonylation processes.[9] While widely used and applicable to many substrates, these methods often require strong acidic conditions or reagents that restrict the variety of functional groups that are tolerated. Complex benzocyclic ketones have been synthesized by derivatization of simple indanones and tetralones,[10] or via indirect, highly specific routes to key targets.[7,11]

Recently, we reported the novel carbopalladation of a cyano group, observing for the first time the addition of alkenyl- and alkylpalladium species across the carbon–nitrogen triple bond of arenenitriles.[12] This process afforded a convenient synthesis of carbocycles, such as indenones and 2-aminonaphthalenes, by the palladium-catalyzed annulation of aromatic nitriles. Herein, we wish to report that the palladium-catalyzed cyclization of appropriately substituted ω-(2-iodoaryl)alkanenitriles has been found to be an efficient and general route to 2,2-disubstituted indanones (**I**, $n=1$) and related benzocyclic ketones (Eq. (1)).



I II (1)

Our initial attempt to apply our previous nitrile annulation conditions[12] to the cyclization of 2,2-dimethyl-3-(2-iodophenyl)propanenitrile (**1**) met with only partial success as GC–MS analysis of the reaction mixture after 24 h revealed the presence of approximately equal amounts of the target, 2,2-dimethyl-1-indanone (**2**), and unreacted **1**. A longer reaction time failed to change this ratio or bring about more complete conversion of the starting material. We then focused our optimization efforts on reaction conditions similar to those employed by Yang et al. in their study of the intramolecular addition of an arylpalladium to a proximal alkenenitrile.[13] The following optimal reaction conditions have subsequently been established: 0.25 mmol of the ω-(2-iodoaryl)alkanenitrile, 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, and 1.2 equiv. of NEt_3 in 5 ml of a 9:1 DMF–water mixture are stirred at 130°C under Ar for an appropriate amount of time. It should be noted that an inert atmosphere is not essential for the success of the procedure as the product yields decrease only slightly when the reaction is conducted in air. We have also found that formation of the cyclization products is often accompanied by some reduction of the carbon–iodine bond of the starting materials (Eq. (1)),[14] which is not uncommon for palladium-catalyzed reactions of aryl halides.[15] The results of our studies on the scope and limitations of this process are summarized in Table 1.

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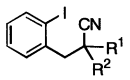
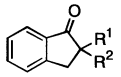
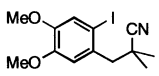
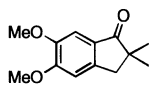
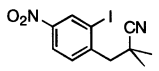
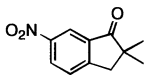
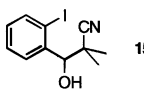
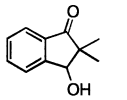
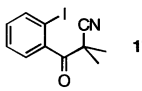
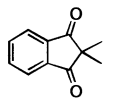
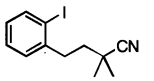
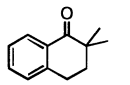
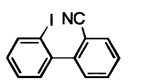
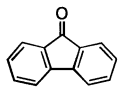
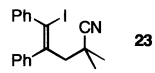
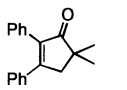
Table 1. Synthesis of benzocyclic ketones by the Pd-catalyzed cyclization of ω-(2-iodoaryl)alkanenitriles (Eq. (1))[a]

entry	nitrile	time (h)	cyclization product (I)	% yield[b] I	% yield[b] II
					
1	R^1,R^2 = Me (**1**)	12	**2**	88	12
2	R^1,R^2 = -$(CH_2)_5$- (**3**)	12	**4**	86	8
3	R^1,R^2 = Ph (**5**)	15	**6**	92	7
4	R^1 = H, R^2 = Et (**7**)	12	**8**	30	50
5	R^1 = Me ,R^2 = CO_2Me (**9**)	12	**10**	78, 73[c]	trace
6	 **11**	29	 **12**	75[c]	trace
7	 **13**	12	 **14**	35	64
8	 **15**	12	 **16**	80	5
9	 **17**	15	 **18**	83	6
10	 **19**	24	 **20**	69	16
11	 **21**	12	 **22**	56	24
12	 **23**	12	 **24**	94[c]	0

[a] All reactions were carried out under the previously described optimal conditions.
[b] Yields determined by ^{1}H NMR spectral analysis unless specified otherwise.
[c] Isolated yield.

Under the optimized reaction conditions, **1** readily cyclizes to afford 2,2-dimethyl-1-indanone (**2**) in a high yield (Table 1, entry 1). Equally successful is the cyclization of 1-(2-iodobenzyl)cyclohexanecarbonitrile (**3**), producing the spirocyclic indanone **4** (entry 2), the skeleton of which is related to several pharmaceutical substances.[1a,3b,4a] 2,2-Diphenyl-1-indanone (**6**) was obtained in a 92% yield (entry 3), despite our concern that 2-aryl-3-(2-iodophenyl)propanenitriles might undergo a potential side reaction whereby the initially obtained arylpalladium intermediate (see the proposed mechanism below) would couple with one of the aryl substituents to afford a dihydrophenanthrene derivative.[16] Cyclization of the secondary nitrile **7** resulted in only a modest yield of the target 2-ethyl-1-indanone (**8**, entry 4). The major product proved to be the dehalogenated starting material. This represents a limitation of the current procedure, as so far no conditions have been found that substantially increase the yield of 2-monosubstituted indanones. However, this limitation can be overcome by the decarboxylation of 1-indanone-2-carboxylate esters,[17] such as **10**, which is readily prepared from methyl 2-cyano-3-(2-iodophenyl)-2-methylpropanoate (**9**) using our cyclization procedure (entry 5).

The cyclization seems to be reasonably general with respect to the substituents in the alkyl chain and the aromatic ring (entries 1–9) and tolerant of a variety of functional groups (entries 5–9). The indanones **10**, **12**, **14**, **16** and **18** have been obtained from the corresponding substrates containing ester, ether, nitro, hydroxy and keto functionalities. The electron-rich aryl iodide **11** produced the corresponding indanone **12** in a yield comparable to that obtained with the parent system **1**, although this cyclization required a longer reaction time (entry 6), presumably due to the more sluggish oxidative addition of **11** to the Pd(0) catalyst. The lower yield

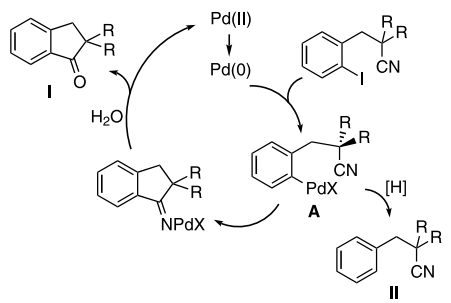
in the cyclization of the electron-poor nitrile **13** (entry 7) is probably caused by the reduced nucleophilicity of the arylpalladium intermediate involved in attack on the cyano group (vide infra).

The current cyclization appears to be applicable to the synthesis of benzocyclic ketones other than indanones. Thus, 4-(2-iodophenyl)-2,2-dimethylbutanenitrile (**19**) has been found to afford tetralone **20** in a good yield (entry 10). The efficacy of this cyclization in six-membered ring formation is remarkable considering that the greater conformational flexibility present in **19** must significantly reduce the likelihood of achieving the conformation necessary for intramolecular addition of the arylpalladium to the cyano group.

Other cyclic ketones can be readily prepared by this methodology. For example, 9-fluorenone (**22**) was obtained from the biaryl substrate **21** in what we believe to be the first example of the addition of an *aryl*palladium to an *arene*nitrile (entry 11). Finally, the reaction scope has been extended to include the vinylic substrate **23**, the cyclization of which resulted in the formation of the cyclopentenone **24** in high isolated yield (entry 12).

We propose the mechanism illustrated in Scheme 1 for this palladium-catalyzed cyclization of ω-(2-iodoaryl)alkanenitriles. Oxidative addition of the aryl iodide to a Pd(0) species, produced by reduction of $Pd(OAc)_2$, leads to the arylpalladium intermediate **A**. The next step, carbopalladation, requires sufficient electron density on the palladium center in **A** for it to add to the carbon–nitrogen triple bond, as well as close proximity of the cyano group to this palladium center (i.e. the conformation shown in Scheme 1). Addition of the arylpalladium species **A** across the cyano group affords an iminopalladium intermediate, which then hydrolyzes to the corresponding ketone **I**. The Pd(II) is then reduced again to Pd(0) that returns to the catalytic cycle. Alternatively, the arylpalladium intermediate **A** may undergo a reduction process, which results in formation of the byproduct **II**. The exact mechanism of this reduction, as well as the identity of the reagent responsible for reducing intermediate **A** or for reduction of Pd(II) to Pd(0), are unknown at this time.

In conclusion, we have developed a general and efficient method for the synthesis of 2,2-disubstituted benzocyclic ketones from readily prepared ω-(2-iodoaryl)alkanenitriles. The procedure tolerates a wide variety of functional groups and may be adapted for the indirect synthesis of 2-monosubstituted indanones. The suitability of this methodology for the preparation of a 9-fluorenone and a cyclopentenone has also been demonstrated.



Scheme 1.

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