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Multistep synthesis of a new tricyclic azaindole-based scaffold

Mauro Angiolini *, Andrea Lombardi Borgia, Tiziano Bandiera †

Nerviano Medical Sciences Srl, Viale Pasteur 10, 20014 Nerviano, Milano, Italy

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ABSTRACT

In this Letter the synthetic pathway adopted for the preparation of a new functionalized tricyclic scaffold containing the 7-azaindole moiety is presented. An intramolecular palladium-mediated reaction is described as the crucial step for a condensed seven-membered ring formation.

The chemistry of indole heterocycles is of great interest to the pharmaceutical industry as several biological properties are associated with this chemical core in therapeutic areas such as central nervous system, inflammation and cancer. Recently, 7-azaindoles, which share with indoles the same [4.3]-bicyclic indene architecture, but contain a second nitrogen atom in the six-membered ring, have received increasing attention both as indole replacement and as a scaffold endowed with peculiar physico-chemical and biological activities (Fig. 1).[1]

As part of our research activity in the field of kinase inhibitors, we became interested in the design of new scaffolds containing the 7-azaindole core as the binding motif to kinase hinge region.[2] In particular we focused our attention on tricyclic compounds having general formula **A**, where the presence of a condensed seven-membered ring makes the structure synthetically challenging to prepare. (Fig. 1).

We envisaged a retro-synthetic approach where the tricyclic scaffold is generated by ring-closure of a suitably functionalized 7-azaindole derivative, as depicted in Scheme 1. The key step of the synthesis is represented by the intramolecular Heck cyclization of intermediate **B** between the terminal electron-poor double bond, since R' is a carboxylic ester function, and the aromatic halide installed at C-3 of the azaindole.[3]

As a first approach to compound **B** (R = R′ = COOMe, X = H), we tried the introduction of a dimethyl-malonate group at C-4 position of the 7-azaindole by a copper-mediated reaction. However

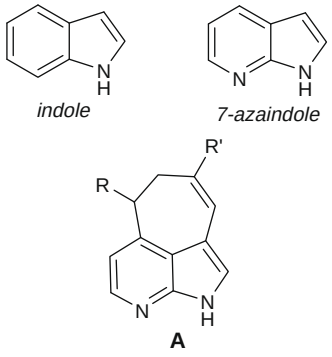
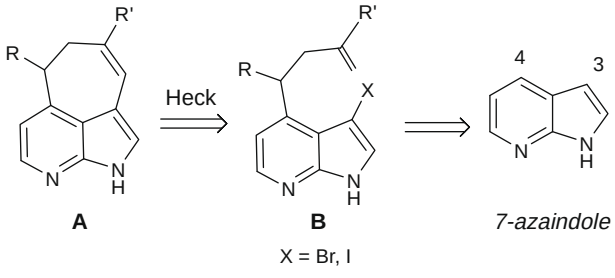


Figure 1. Chemical structures of indole, 7-azaindole and compound A.



Scheme 1. Retro-synthetic approach for compound A.

* Corresponding author. Tel.: +39 0331581518; fax: +39 0331581347.
E-mail address: mauro.angiolini@nervianoms.com (M. Angiolini).
† Present address: Istituto Italiano di Tecnologia, via Morego 30, 16163 Genova, Italy.

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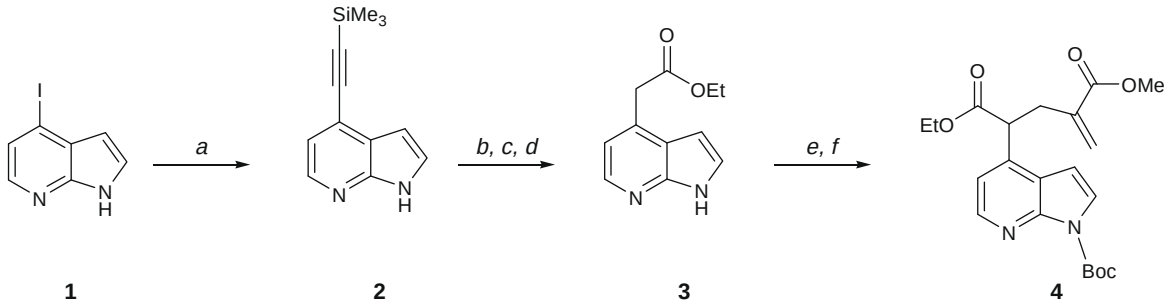


Scheme 2. Reagents and conditions: (a) TEA, CuI, trimethylsilylacetylene, $PdCl_2(Ph_3P)_2$, rt, 2 h, 80%; (b) $BH_3{\cdot}SMe_2$, THF, cyclohexene, 0 °C to rt, 1.5 h; (c) $NaHCO_3$, H_2O_2, 0 °C to rt, 18 h; (d) EtOH, H_2SO_4, rt, 18 h, 55% over three steps; (e) THF, DMAP, $(Boc)_2O$, rt, 6 h, 70%; (f) THF, LiHMDS 1 M in THF, 2-bromomethyl-acrylic acid methyl ester, −78 °C, 1 h, 90%.

the reaction did not work at all prompting us to design a new synthetic pathway.[4]

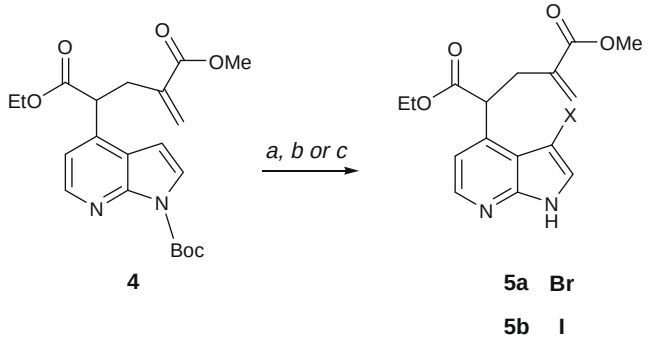
We then turned to a Sonogashira coupling reaction between 4-iodo-azaindole **1** and trimethylsilylacetylene. The coupling worked satisfactorily affording compound **2** in 80% yield, as reported in Scheme 2. The intermediate **2** was manipulated through several steps aiming to convert the triple bond into an aryl-acetic moiety. Thus, hydroboration of the triple bond followed by an oxidative work-up with hydrogen peroxide and sodium bicarbonate furnished the corresponding aryl-acetic compound, which in turn was converted into the ethyl ester **3** with ethanol in the presence of sulfuric acid as catalyst. The protection of the nitrogen in position 1 as Boc-derivative made possible a highly efficient alkylation of the benzylic position at C-4 with LiHMDS as base at −78 °C and bromomethyl-acrylic acid methyl ester, affording the highly functionalized compound **4** in good yield (Scheme 2).[5–7]

With derivative **4** in our hands, an electrophilic addition at C-3 position allowed the introduction of the halogen atom necessary for the planned intramolecular Heck reaction. Deprotection of the Boc group with trifluoroacetic acid and reaction with NBS or NIS in dry DMF afforded the corresponding bromo- or iodo-derivatives 5a–b in 70% yield, enabling us to finally carry out the cyclization step for seven-membered ring formation (Scheme 3).

Several cyclization attempts were carried out on both the 3-bromo- and 3-iodo-derivatives **5a** and **5b** using different conditions and catalysts as summarized in Table 1.

The data confirmed that the seven-membered ring cyclization, as expected, was a critical step and the Herrmann–Beller catalyst, a palladacycle derivative commercially available, allowed the isolation of the tricyclic scaffold **6** in 30% yield in a DMF–water solvent mixture at 130 °C and with Bu_4NOAc, as depicted in Scheme 4.

The direction of cyclization is controlled by the electron-withdrawing nature of the carboxylic ester function installed on the

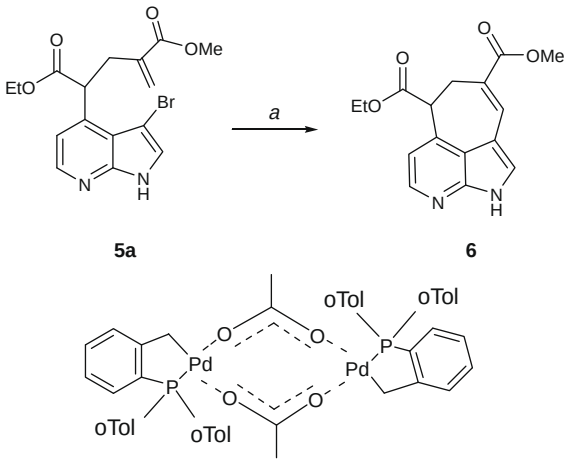


Scheme 3. Reagents and conditions: (a) DCM, TFA, rt, 4 h, 90%; (b) DMF, NBS, rt, 1 h, 70%; (c) DMF, NIS, rt, 1 h, 70%.

Table 1
Experimental conditions for the Heck reaction.

Entry	1	2	3	4
Solvent	DMF	DMF	Toluene	DMF–H_2O
Catalyst	$Pd(PPh_3)_4$	$Pd(OAc)_2$	$Pd(OAc)_2$	Herrmann
% Cat.	5	10	5	7
Halogen	I	Br	I	Br
Base	Ag_3PO_4	K_2CO_3	TEA[a]	Bu_4NOAc
T (°C)	90	90	90	130
Yield (%)	Trace	20	—	30

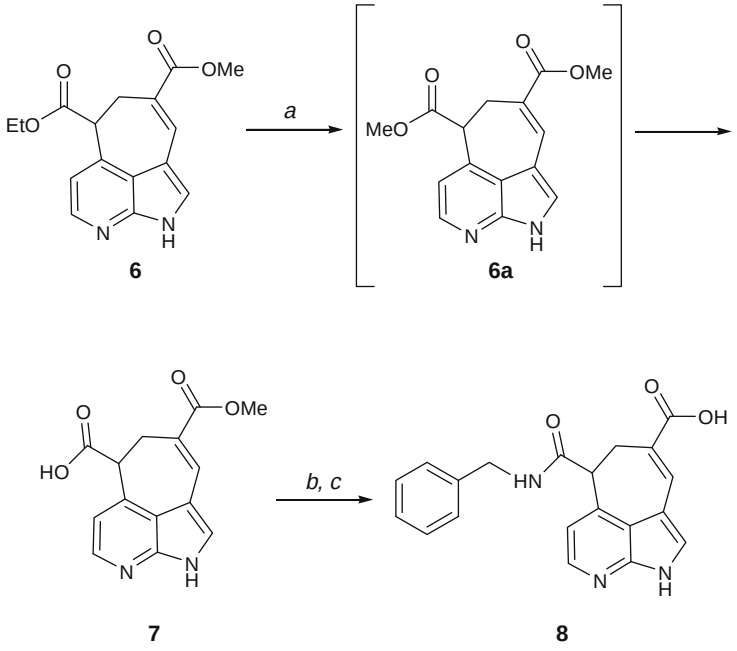
[a] The reaction was carried out in the presence of P(*o*-Tolyl)$_3$.



Scheme 4. Reagents and conditions: (a) DMF–H_2O 5:1, 7% Herrmann–Beller catalyst, 130 °C, Bu_4NOAc, 8 h, 30%.

terminal double bond, which determined the *endo* closure and formation of the seven-membered ring. A different catalyst such as palladium-(bis)acetate also gave the expected product but only with 20% yield in DMF as solvent and K_2CO_3 as base. Finally palladium tetrakis furnished only a trace of the product **6** when the compound **5b** was the substrate for cyclization. In fact in this case the reaction led to the corresponding de-ionidated compound as the main reaction by-product. In any case, the bromo-derivative **5a** revealed to be the best substrate for the cyclization step.[8,9]

At this point our synthetic scheme required the selective transformation of the two ester moieties, aiming to prepare an initial derivative as a model compound for testing activities. Thus we carried out, through a fast trans-esterification reaction to the corre-



Scheme 5. Reagents and conditions: (a) THF–H_2O–MeOH 3:1:1, LiOH, rt, 72 h, 85%; (b) DCM, TEA, TBTU, benzylamine, rt, 2 h, 85%; (c) LiOH, MeOH, rt, 18 h, 80%.

sponding dimethyl ester intermediate **6a**, the complete and selective hydrolysis of the more reactive aliphatic ester with 2 equiv of LiOH in a methanol–water–THF mixture. The reaction was quite clean and furnished slowly the monoacid compound **7** in good yield by a simple one-pot procedure. Subsequent coupling of intermediate **7** with benzylamine in DCM with TBTU and further hydrolysis of the α,β-unsaturated ester moiety with 10 equiv of LiOH afforded the representative amide monoacid derivative **8**, proving that the new tricyclic scaffold can also be easily functionalized by simple chemical manipulation (Scheme 5).

In conclusion, we have described the preparation of a new functionalized tricyclic scaffold containing the 7-azaindole core by a multistep synthesis. The crucial cyclization reaction to the seven-membered ring was accomplished in acceptable yield by employing the Herrmann–Beller palladacycle catalyst. The two carboxylic ester functions could be differentiated taking advantage of the higher reactivity of the saturated vis-a-vis the α,β-unsaturated ester. In fact complete and selective hydrolysis of the aliphatic ester led to the versatile intermediate **7**. This compound is amenable to further manipulation by exploiting the chemistry of carboxylic functional group, thus opening opportunities for a diversity-oriented synthesis. Moreover the tricyclic scaffold represents a novel pharmacophore with attractive and original profile.

References and notes

1. (a) Bartberger, M. D.; Sukits, S.; Wilde, C.; Soukup, T. *Synthesis* **2008**, 201–214; (b) Popowycz, F.; Routier, S.; Joseph, B.; Mérour, J. Y. *Tetrahedron* **2007**, *63*, 1031–1064; (c) Mérour, J. Y.; Benoît, J. *Curr. Org. Chem.* **2001**, *5*, 471–506.
2. (a) Seefeld, M. A.; Rouse, M. B.; McNulty, K. C.; Sun, L.; Wang, J.; Yamashita, D. S.; Luengo, J. I.; Zhang, S. Y.; Minthorn, E. A.; Concha, N. O.; Heerding, D. A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2244–2248; (b) Kim, K. S.; Zhang, L.; Schmidt, R.; Cai, Z. W.; Wei, D.; Williams, D. K.; Lombardo, L. J.; Trainor, G. L.; Xie, D.; Zhang, Y.; An, Y.; Sack, J. S.; Tokarski, J. S.; Darienzo, C.; Kamath, A.; Marathe, P.; Zhang, Y.; Lippy, J.; Jeyaseelan, R., Sr.; Wautlet, B.; Henley, B.; Gullo-Brown, J.; Manne, V.; Hunt, J. T.; Fargnoli, J.; Borzilleri, R. M. *J. Med. Chem.* **2008**, *51*, 5330–5341; (c) Tang, J.; Hamajima, T.; Nakano, M.; Sato, H.; Dickerson, S. H.; Lackey, K. E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4610–4614; (d) Casuscelli F.; Casale, E.; Faiardi, D.; Piutti, C.; Mongelli, N.; Traquandi, G. Patent Application EP2002836, 2008.
3. (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581; (b) Heck, R. F., ; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320–2322; (c) Beletskaja, P. I.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.
4. (a) Yip, S. F.; Cheung, H. Y.; Zhou, Z.; Kwong, F. Y. *Org. Lett.* **2007**, *9*, 3469–3472; (b) Hennessy, E. J.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 269–272.
5. Caldwell, J. J.; Cheung, K. M.; Collins, I. *Tetrahedron Lett.* **2007**, *48*, 1527–1529.
6. Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874–922.
7. (a) Torisu, K.; Kobayashi, K.; Iwahashi, M.; Nakai, Y.; Onoda, T.; Nagase, T.; Sugimoto, I.; Okada, Y.; Matsumoto, R.; Nanbu, F.; Ohuchida, S.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2004**, *12*, 4685–4700; (b) Alemany, C.; Bach, J.; Garcia, J.; Lopez, M.; Rodriguez, A. B. *Tetrahedron* **2000**, *56*, 9305–9312.
8. (a) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C. P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem.* **1995**, *107*, 1989–1992; (b) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C. P.; Priermeier, T.; Beller, M. *Chem. Eur. J.* **1997**, *3*, 1354–1367; (c) Tietze, L. F.; Schirok, H.; Wöhrmann, M.; Schrader, K. *Eur. J. Org. Chem.* **2000**, 2433–2444.
9. *Experimental procedure for the synthesis of compound* ***6*** *by the intramolecular Heck reaction*: To a 0.025 M solution of compound **5a** (0.736 mmol, 1 equiv) in a mixture of 5:1 DMF–H_2O under argon atmosphere, the catalyst (0.05 mmol, 0.07 equiv) and NBu_4AcO (2.65 mmol, 3.6 equiv) were added. The mixture was stirred at 130 °C for 8 h and treated with ethyl acetate, dried over Na_2SO_4, and evaporated to dryness. The crude was purified by flash column chromatography (AcOEt/hexane 1:1) affording the title compound as white solid in 30% yield. MS–ESI for $C_{16}H_{17}N_2O_4$ (MH^+): 301.18; MS–ESI for $C_{16}H_{15}N_2O_4$ (MH^-): 299.16. ^1H NMR (400 MHz, $CDCl_3$): δ 1.18 (t, 3H, J = 5.5 Hz), 2.92 (d, 1H, J = 5.8 Hz), 3.84 (s, 3H), 4.15 (m, 3H), 4.37 (dd, 1H, J = 5.8 and 1.2 Hz), 7.22 (d, 1H, J = 5.1 Hz), 7.64 (s, 1H), 7.85 (s, 1H), 8.17 (d, 1H, J = 5.1 Hz), 12.11 (br s, 1H).