Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4123–4126

A facile synthetic route to new pyrazoloisoindolones

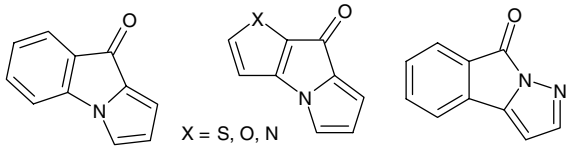
Anne-Laure Gérard, Clément Mahatsekake, Valérie Collot and Sylvain Rault*

Centre d'Etudes et de Recherche sur le Médicament de Normandie, UFR des Sciences Pharmaceutiques, 5 rue Vaubénard, 14032 CAEN Cedex, France

Received 12 February 2007; revised 29 March 2007; accepted 2 April 2007
Available online 6 April 2007

Abstract—A facile method for the synthesis of new pyrazoloisoindolones via a Suzuki cross-coupling reaction using a pyrazolylboronic ester is described.

Pyrazoloisoindolone derivatives are known for their plant growth regulating properties.[1] These structures can be regarded as aza-pyrroloindolones or aza-analogues of tripentones which possess anti-cancer properties and which are widely studied in our laboratory.[2] This is the reason why we investigated the synthesis of such tricyclic compounds.



Pyrroloindolone Tripentones Pyrazoloisoindolone

Very few studies are devoted to pyrazoloisoindolones compared to pyrroloindolones. However, the synthesis of some pyrazoloisoindolones is described in the literature either by condensation of 3-(2-oxo-2-arylethyl)-2-benzofuranone with hydrazine[3] or by reaction of iminophosphoranes with acetylenic compounds[4] or by intramolecular Wittig reaction of phosphorus ylides.[5] In an interesting way Bousquet[3b] obtained 2-arylpyrazoloisoindolones by condensation of hydrazine with benzofuranone followed by dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and further to these works, Johnson[6] reported that these pyrazoloisoindolones were very susceptible to nucleophilic attack at the lactam function. So, pyrazoloisoindolones are cleaved to 2-[3(5)-arylpyrazol-3(5)-yl]benzoic acid derivatives with aqueous bases, alcohols or amines. The reverse cyclisation proceeded with thionyl dichloride, phosphoric trichloride or acetic anhydride.[7]

All these methods give access to a variety of 2- and/or 3-substituted pyrazoloisoindolones, but only two references mentioned pyrazoloisoindolones substituted on phenyl ring.[8] In view of this lack of studies, we wished to develop a facile and rapid method to obtain new pyrazoloisoindolones.

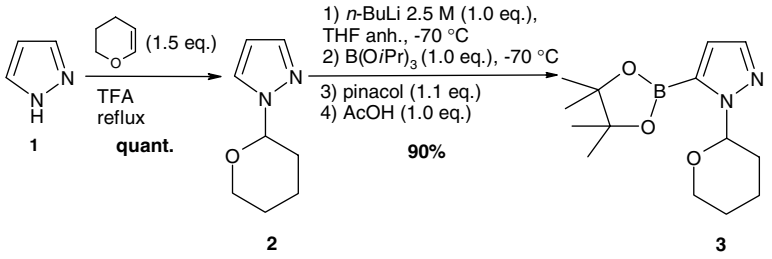
We recently published the synthesis of 3(5)-aryl-1*H*-pyrazoles by reaction of a pyrazolylboronic ester with aryl halides.[9] With the aim of emphasizing our works and in the light of the work of Johnson,[6] we decided to investigate the intramolecular cyclisation of 4- and 5-substituted-2-(1*H*-pyrazol-3(5)-yl)benzoic acid derivatives. In this paper, we present our first results concerning this methodology which allows an easy access to new 5- and 6-substituted pyrazoloisoindolones.

The first step consisted in an N-protection of 1*H*-pyrazole with a stable protecting group under lithiation conditions but easy to cleave under acid conditions. We recently demonstrated that THP was an excellent pyrazole N-protecting group since it has these properties, it orients the lithiation at C-5 position and stabilizes the lithio intermediate.[9] So tetrahydropyran moiety was introduced by reacting pyrazole with dihydropyran and we obtained 1-THP-1*H*-pyrazole **2** in quantitative yield (Scheme 1).[9,10]

This protected pyrazole **2** was then engaged in the lithiation reaction using 1 equiv of 2.5 M *n*-butyllithium in anhydrous THF at −70 °C. The lithio pyrazole was then

Keywords: Pyrazoloisoindolones; Pyrazolylboronic ester; Suzuki cross-coupling reaction.
* Corresponding author. Tel.: +33 2 31 56 59 10; fax: +33 2 31 93 11 88; e-mail: sylvain.rault@unicaen.fr

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.04.004



Scheme 1.

reacted with triisopropylborate ($B(OiPr)_3$) and transesterified with pinacol to finally give the expected 1-THP-1*H*-pyrazolylboronic ester **3** in an excellent yield (Scheme 1).

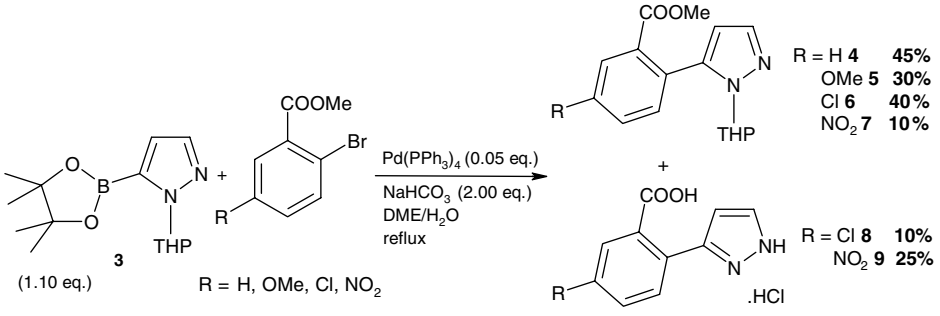
Boronic ester **3** was then coupled with different commercially available methyl 2-bromobenzoates under standard Suzuki cross-coupling reaction type conditions (Scheme 2).[9,11] Corresponding esters **4** and **5** were obtained in, respectively, 45% and 30% yields. With these cross-coupling reaction conditions we obtained esters **6** and **7** as well as the corresponding deprotected acids **8** and **9**.

Deprotected acids **8** and **9** were then engaged in an intramolecular cyclisation with thionyl dichloride. After 1 h refluxing in dichloromethane, the cyclisation proceeded in good yields and gave 6-chloro **10** and 6-nitropyrazoloisoindolones **11** as yellow solids in, respectively, 87% and 50% yields (Scheme 3).

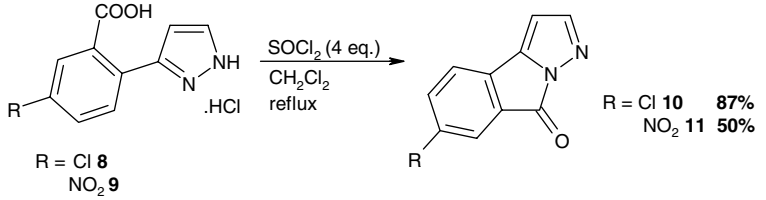
Because THP protecting group is labile under acid conditions, we wanted to obtain protected acids from esters **4** and **5** and then study the deprotection and cyclisation in a one step procedure.

Protected esters **4** and **5** were saponified under basic conditions with an aqueous sodium hydroxide solution to give the protected acids **12** and **13** in 50% yields. Conversion to pyrazoloisoindolones **14** and **15** with thionyl dichloride in boiling dichloromethane was successful and gave the unsubstituted pyrazoloisoindolone **14** in 55% yield and 6-methoxypyrazoloisoindolone **15** in 90% yield (Scheme 4).

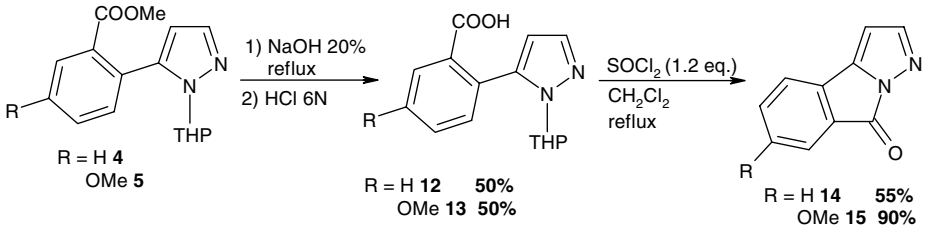
These results encouraged us to enlarge this methodology to the 5-substituted series. We described herein the synthesis of the 5-fluoropyrazoloisoindolone. The first step consisted in the preparation of methyl 2-bromo-4-fluorobenzoate **16** by esterification of the commercially corresponding acid with thionyl dichloride in refluxing methanol. Product **16** reacted with boronic ester **3**, tetrakis(triphenylphosphine)palladium and sodium hydrogen carbonate in a mixture of DME/H_2O to give the corresponding protected ester **17** and acid **18** in moderate yields (Scheme 5).



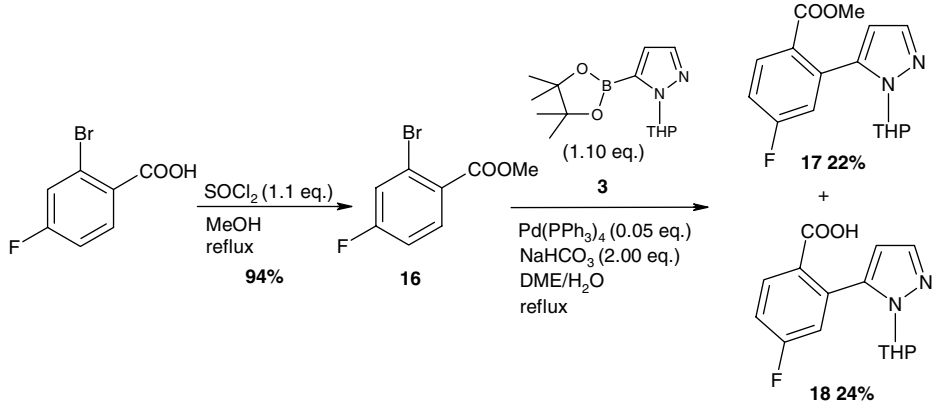
Scheme 2.



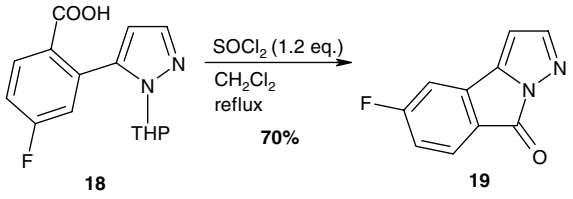
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

In a similar manner as for compounds **12** and **13**, acid **18** underwent a cyclisation with thionyl dichloride in boiling dichloromethane to form yellow 5-fluoro-8*H*-pyrazolo[5,1-*a*]isoindol-8-one **19** in 70% yield (Scheme 6).[12]

To conclude we have described a rapid, facile and efficient method to prepare new pyrazoloisoindolones[12,13] via Suzuki cross-coupling reaction using a pyrazolylboronic ester. These very promising results encourage us to pursue our studies with the aim of obtaining several new pyrazoloisoindolones with therapeutic interest.

Acknowledgements

We thank Sanofi-Aventis laboratories and the 'Conseil Régional de Basse-Normandie' for their financial support and Dr. Christophe Philippo for helpful discussions.

References and notes

1. (a) Toja, E.; Omodei-Sale, A.; Cattaneo, C.; Galliani, G. *Eur. J. Med. Chem.* **1982**, *17*, 223–227; (b) Johnson, A. L. U.S. Patent 3,849,436, 1974; (c) Johnson, A. L.; Sweetser, P.B. DE 2219702, 1972; (d) Beyer, E. M.; Johnson, A. L.; Sweetser, P. B. *Plant Physiol.* **1976**, *57*, 839–841; (e) Katekar, G. F.; Geissler, A. E. *Plant Physiol.* **1980**, *66*, 1190–1195; (f) Katekar, G. F.; Navé, J.-F.; Geissler, E. *Plant Physiol.* **1981**, *68*, 1460–1464.
2. (a) Lisowski, V.; Enguehard, C.; Lancelot, J.-C.; Caignard, D.-H.; Lambel, S.; Léonce, S.; Pierre, A.; Atassi, G.; Renard, P.; Rault, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2205–2208; (b) Lisowski, V.; Léonce, S.; Kraus-Berthier, L.; Sopková-de Oliveira Santos, J.; Pierré, A.; Atassi, G.; Caignard, D.-H.; Renard, P.; Rault, S. *J. Med. Chem.* **2004**, *47*, 1448–1464; (c) Rochais, C.; Lisowski, V.; Dallemagne, P.; Rault, S. *Bioorg. Med. Chem.* **2006**, *14*, 8162–8175.
3. (a) McKusick, B. C. Ger. Offen. 2161180, 1972; (b) Bousquet, E. W.; Moran, M. D.; Harmon, J.; Johnson, A. L.; Summers, J. C. *J. Org. Chem.* **1975**, *40*, 2208–2211.
4. Merot, P.; Gadreau, C.; Foucaud, A. *Tetrahedron* **1981**, *37*, 2595–2599.
5. Islami, M. R.; Abedini-Torghabeh, J.; Fatemi, S. J.; Hassani, Z.; Amiry, A. *Synlett* **2004**, *10*, 1707–1710.
6. Johnson, A. L.; Sweetser, P. B. *J. Org. Chem.* **1976**, *41*, 110–114.
7. Voitenko, Z. V.; Pokholenko, O. A.; Kondratov, I. S.; Kovtunenko, V. O.; André, C.; Wolf, J. G. *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, *180*, 163–177.
8. (a) Chupp, J. P.; Leo, G. C.; Molyneaux, J. M. *J. Heterocycl. Chem.* **1991**, *28*, 613–617; (b) Johnson, A. L.; Sweetser, P. B. U.S. Patent 3,948,937, 1976.

9. Gérard, A.-L.; Bouillon, A.; Mahatsekake, C.; Collot, V.; Rault, S. *Tetrahedron Lett.* **2006**, *47*, 4665–4669.
10. Young, M. B.; Barrow, J. C.; Glass, K. L.; Lundell, G. F.; Newton, C. L.; Pellicore, J. M.; Rittle, K. E.; Selnick, H. G.; Stauffer, K. J.; Vacca, J. P.; Williams, P. D.; Bohn, D.; Clayton, F. C.; Cook, J. J.; Krueger, J. A.; Kuo, L. C.; Lewis, S. D.; Lucas, B. J.; McMasters, D. R.; Miller-Stein, C.; Pietrak, B. L.; Wallace, A. A.; White, R. B.; Wong, B.; Yan, Y.; Nantermet, P. G. *J. Med. Chem.* **2004**, *47*, 2995–3008.
11. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168; (c) Kotha, S.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695; (d) Gérard, A.-L.; Lisowski, V.; Rault, S. *Tetrahedron* **2005**, *61*, 6082–6086.
12. *Typical procedure for the synthesis of pyrazoloisoindolones*: *5-fluoro-8H-pyrazolo[5,1-a]isoindol-8-one* (**19**). A solution of **18** (1 g, 3.44 mmol) in CH_2Cl_2 (50 mL) was treated with thionyl dichloride (0.3 mL, 4.13 mmol) and was refluxed under stirring for 1 h. After removing the solvent under reduced pressure, the residue was dissolved in AcOEt (50 mL) and the solution was washed with saturated aqueous sodium hydrogen carbonate solution (50 mL) and water (2×50 mL), dried over $MgSO_4$, filtered and evaporated to give 5-fluoropyrazoloisoindolone **19** as a yellow solid that was crystallized from *n*-hexane. (0.45 g, 70%); mp 164 °C; IR (KBr): 3119, 3042, 1755 (CO), 1622, 1585, 1472, 1407, 1335, 1306, 1289, 1220, 1188, 1161, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (dd, 1H, $J = 8.3$, 4.9 Hz, H_{phenyl}), 7.73 (d, 1H, $J = 1.3$ Hz, H_2), 7.15 (dd, 1H, $J = 7.8$, 2.2 Hz, H_{phenyl}), 7.06 (td, 1H, $J = 8.5$, 2.2 Hz, H_{phenyl}), 6.38 (d, 1H, $J = 1.3$ Hz, H_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.02 (d, $^1J = 255$ Hz), 158.84, 149.39, 144.76, 134.59 (d, $^3J = 10.7$ Hz), 128.78 (d, $^3J = 10.7$ Hz), 127.18 (d, $^4J = 3.3$ Hz), 116.19 (d, $^2J = 23.1$ Hz), 109.81 (d, $^2J = 25.6$ Hz), 103.55; HRMS Calcd for $C_{10}H_5FN_2O$, 188.0386; found, 188.0377. Anal. Calcd for $C_{10}H_5FN_2O$: C, 63.83; H, 2.68; N, 14.89. Found: C, 63.68; H, 2.56; N, 14.67.
13. *Spectroscopic data for novel pyrazoloisoindolones: 6-chloro-8H-pyrazolo[5,1-a]isoindol-8-one* (**10**): yellow solid (0.14 g, 87%); mp 132 °C; IR (KBr): 3097, 1766 (CO), 1618, 1578, 1455, 1419, 1316, 1277, 1167, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, 1H, $J = 1.9$ Hz, H_7), 7.72 (d, 1H, $J = 1.2$ Hz, H_2), 7.53 (dd, 1H, $J = 8.0$, 1.9 Hz, H_5), 7.37 (d, 1H, $J = 8.0$ Hz, H_4), 6.35 (d, 1H, $J = 1.2$ Hz, H_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.67, 149.88, 145.50, 135.94, 134.61, 133.11, 130.14, 126.92, 122.32, 103.24; HRMS Calcd for $C_{10}H_5ClN_2O$, 204.0090; found, 204.0082. *6-Nitro-8H-pyrazolo[5,1-a]isoindol-8-one* (**11**): yellow solid (0.32 g, 50%); mp 199 °C; IR (KBr): 3142, 3101, 1769 (CO), 1621, 1528, 1342, 1276, 1201, 1145, 1063 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, 1H, $J = 2.2$ Hz, H_7), 8.50 (dd, 1H, $J = 8.3$, 2.2 Hz, H_5), 7.83 (d, 1H, $J = 1.3$ Hz, H_2), 7.65 (d, 1H, $J = 8.3$ Hz, H_4), 6.57 (d, 1H, $J = 1.3$ Hz, H_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.45, 150.30, 148.71, 144.34, 136.90, 132.74, 130.36, 121.79, 121.77, 105.32; LCMS (ESI) 216 (M+H). Anal. Calcd for $C_{10}H_5N_3O_3$: C, 55.82; H, 2.34; N, 19.53. Found: C, 55.55; H, 2.19; N, 19.33. *8H-Pyrazolo[5,1-a]isoindol-8-one* (**14**): yellow solid (0.17 g, 55%); mp 158 °C; IR (KBr): 3136, 3107, 1746 (CO), 1618, 1579, 1469, 1426, 1328, 1309, 1273, 1207, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, 1H, $J = 7.5$ Hz, H_{phenyl}), 7.71 (d, 1H, $J = 1.5$ Hz, H_2), 7.56 (td, 1H, $J = 7.5$, 1.2 Hz, H_{phenyl}), 7.43 (d, 1H, $J = 8.0$ Hz, H_{phenyl}), 7.39 (td, 1H, $J = 7.5$, 0.9 Hz, H_{phenyl}), 6.34 (d, 1H, $J = 1.5$ Hz, H_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.97, 149.49, 146.25, 134.86, 132.01, 131.48, 129.63, 126.54, 121.33, 102.78; LCMS (ESI) 171 (M+H). Anal. Calcd for $C_{10}H_6N_2O$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.35; H, 3.43; N, 16.69. *6-Methoxy-8H-pyrazolo[5,1-a]isoindol-8-one* (**15**): yellow solid (0.6 g, 90%); mp 154 °C; IR (KBr): 3095, 2948, 1764 (CO), 1615, 1579, 1483, 1425, 1326, 1289, 1249, 1203,1143 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1 H, $J = 1.3$ Hz, H_2); 7.32 (m, 2H, H_{phenyl}); 7.02 (dd, 1H, $J = 8.3$, 2.4 Hz, H_{phenyl}); 6.21 (d, 1H, $J = 1.3$ Hz, H_3); 3.86 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.15, 159.98, 149.68, 146.64, 133.42, 124.34, 122.50, 119.91, 112.31, 101.70, 55.88; LCMS (ESI) 201 (M+H). Anal. Calcd for $C_{11}H_8N_2O_2$: C, 66.00; H, 4.03; N, 13.99. Found: C, 65.87; H, 3.86; N, 13.72.