Tetrahedron 67 (2011) 7330–7335

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Synthesis of 1,6-dihydropyrrolo[2,3-*g*]indazoles using Larock indole annulation

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ARTICLE INFO

*Article history:*
Received 1 June 2011
Received in revised form 8 July 2011
Accepted 12 July 2011
Available online 21 July 2011

*Keywords:*
Indazole
Larock indole annulation
Pyrroloindazole
Regioselectivity

ABSTRACT

The synthesis of 1,6-dihydropyrrolo[2,3-*g*]indazole derivatives is described. The indolic ring system is constructed via a Larock palladium-catalyzed annulation using terminal and internal alkynes. Additionally, when using internal alkynes for this reaction, we found that a directing effect on regioselectivity was mediated by the ester group of alkyl 3-substituted propiolate derivatives.



## 1. Introduction

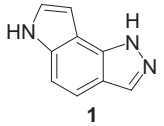
The palladium-catalyzed annulation of internal alkynes proved to be a useful method to access 2,3-disubstituted indole derivatives. Thus, Larock indolization led efficiently to this ring system from 2-iodoaniline derivatives by internal alkyne insertion to an arylpalladium bond and subsequent cyclization of the vinylpalladium intermediate.[1–4] Alternatively, 2,3-disubstituted indoles were synthesized from 2-iodotrifluoroacetanilides and terminal alkynes by Sonogashira cross-coupling and Cacchi reaction sequence: the *o*-alkynyltrifluoroacetanilide obtained after Sonogashira reaction underwent a Pd(II)-catalyzed cyclization in the presence of an arylpalladium(II) species, leading, after reductive elimination of the generated aryl-(indol-3-yl)palladium intermediate, to a product substituted at the 3-position of the indolic ring system by an aryl group.[5–8] In the absence of the catalytic arylpalladium complex, the indol-3-ylpalladium intermediate formed by Pd(II)-catalyzed annulation of *o*-alkynylaniline derivatives can undergo either protonolysis to give 2-substituted indoles, carbonylation, C=C insertion or C=O addition to give 2,3-disubstituted indoles.[3,6,9]

The indole ring system, as well as other nitrogen-containing aromatic heterocyclic systems, plays a wide role in medicinal chemistry, and privileged pharmacophores should be identified in the course of the preparation of novel bioactive small organic molecules. Due to the importance of the indazole ring system in medicinal chemistry,[10] we recently started a research program aimed at developing new compounds containing this heterocyclic system.[11,12] We next focused on the synthesis of new 1,6-dihydropyrrolo[2,3-*g*]indazole derivatives, a heterocyclic system which incorporates an indole subunit (Fig. 1).

There are only a few reports in the literature describing this ring system, which was synthesized either by Fischer indolization or by condensation of hydrazine derivatives with the appropriate 1,3-dicarbonyl indole derivative.[13] The palladium-catalyzed construction of the indole subunit is thought to be complementary and useful to these methods. Therefore, we now report our study on the synthesis of 1,6-dihydropyrrolo[2,3-*g*]indazole derivatives based on a palladium-catalyzed annulation.

## 2. Results and discussion

We started our study from 5,6-dinitroindazole **2**, which was readily obtained from 6-nitroindazole in concentrated sulfuric acid in the presence of potassium nitrate.[12,14] Protection of indazole **2** at the N-1 position by a THP group gave compound **3** in good yield (Scheme 1).[12]




**1**

**Fig. 1.** 1,6-Dihydropyrrolo[2,3-*g*]indazole **1**.

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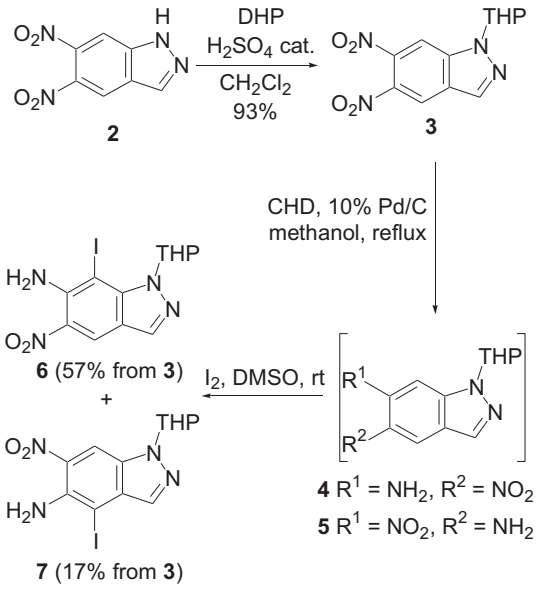
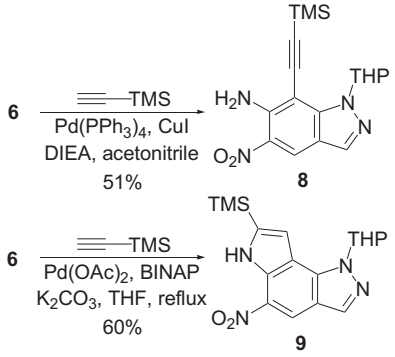
doi:10.1016/j.tet.2011.07.029




**Scheme 1.** Synthesis of *o*-iodoaniline derivatives **6** and **7**.

Access to the pyrroloindazole scaffold implied the selective reduction of one nitro group, subsequent *ortho*-halogenation of the newly prepared arylamine and palladium-catalyzed annulation of the pyrrole nucleus. As we previously reported,[12] both nitro groups of compound **3** can be efficiently reduced in the presence of 10% Pd/C and hydrazine hydrate in refluxing methanol. We found that monoreduction was practicable in refluxing methanol in the presence of 1,4-cyclohexadiene (CHD) as hydrogen donor and 10% Pd/C. After chromatography, an 8:2 inseparable mixture of compounds **4** and **5** was obtained. We next examined the introduction of an iodine atom in *ortho* position to the amino group of compounds **4** and **5**. Initial iodination attempts from **4**/**5** mixture were unsuccessful by using various conditions reported in the literature.[15] Only one method finally gave the iodination products **6** and **7**, by using $I_2$ in DMSO.[16] The products were separable by chromatography to give **6** and **7** in 57% and 17% yields, respectively, from dinitroindazole **3** (Scheme 1). The two regioisomers **6** and **7** were identified by analysis of a $^1H-^1H$ NOESY spectrum. Relevant correlations were found for compound **6** between the two aromatic protons at 8.16 ppm and 8.67 ppm, and for compound **7** between the aromatic proton at 8.58 ppm and the THP anomeric proton at 5.94 ppm.

Having indazole **6** in our hands, we carried on the synthesis by the introduction of an alkynyl side-chain at the 7-position using a Sonogashira cross-coupling. From trimethylsilylacetylene as the terminal alkyne, compound **8** was obtained in 51% yield using $Pd(PPh_3)_4$ in acetonitrile in the presence of CuI and DIEA (Scheme 2).

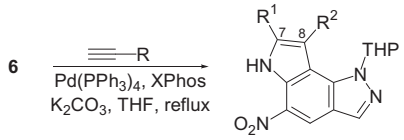



**Scheme 2.** Synthesis compounds **8** and **9**.

Unfortunately, other methods examined to improve the yield of the reaction did not afford the expected Sonogashira product.[17] On the other hand, we found that one of the methods experimented,[17d] using a mixture of $Pd(OAc)_2$, BINAP, and $K_2CO_3$ in refluxing THF, led directly to the desired indole derivative **9** in 60% yield.[18]

We next tried to extend the scope of the reaction to other terminal alkynes but unfortunately, these conditions were only applicable for trimethylsilylacetylene. Nevertheless, by the use of $Pd(PPh_3)_4$/XPhos instead of $Pd(OAc)_2$/BINAP, compound **9** was obtained in 91% yield (entry 1, Table 1). These conditions enabled the preparation of other indole derivatives from compound **6** and other terminal alkynes (Table 1). An excellent 97% yield was obtained when phenylacetylene was used (entry 2). However, a reverse regioselectivity was observed as the phenyl group was found placed at the 3-position of the indolic ring system.[18] This regioselectivity rules out the indole annulation from an alkynyl intermediate. Thus, the synthetic pathway to this indole derivative would probably involve a Larock indolization of phenylacetylene, which to our knowledge has never been reported so far.

**Table 1**
Indolization reaction with terminal alkynes




| Entry | $R^1$ | $R^2$ | Product | Yield (regioisomeric ratio) |
|---|---|---|---|---|
| 1 | TMS | H | **9** | 91% |
| | H | TMS | — | — |
| 2 | Ph | H | — | — |
| | H | Ph | **10** | 97% |
| 3 | *n*-Pr | H | **11** | 96% |
| | H | *n*-Pr | **12** | (**11**/**12** ~ 1:9)[a] |
| 4 | $CH(OEt)_2$ | H | **13** | 65%[b] |
| | H | $CH(OEt)_2$ | **14** | (56% of **14**) |
| 5 | $CH_2OBn$ | H | **15** | 92% |
| | H | $CH_2OBn$ | **16** | (**15**/**16** ~ 3:7)[a] |
| 6 | $CH_2OH$ | H | **17** | 60% |
| | H | $CH_2OH$ | **18** | (~55:45)[a] |
| 7 | $CH_2OAc$ | H | **19** | 95% |
| | H | $CH_2OAc$ | **20** | (~55:45)[a] |

[a] An inseparable mixture of regioisomers was isolated.
[b] A mixture of compounds **13** and **14** was obtained. Compound **14** was the only regioisomer which could be isolated by chromatography, a part remaining in mixture with compound **13**.

The same regioselectivity was observed with other terminal alkynes (entries 3–5).[18] However, the formation of the minor 7-substituted pyrrolo[2,3-*g*]indazole was also detected. Oppositely, the annulation using propargyl alcohol or its acetyl derivative (entries 6 and 7) was not regioselective. Compounds **15**/**16**, **17**/**18**, and **19**/**20** were obtained as inseparable mixtures of regioisomers. The regioisomeric ratios were measured for each mixture according to characteristic $^1H$ NMR peaks.[19]

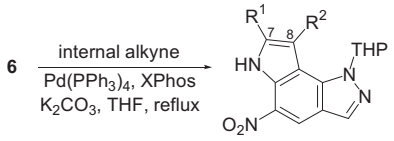
It appeared from our results that, with the exception of trimethylsilylacetylene, the more sterically demanding group was positioned at the 3-position of the indole system, which is not in accordance with the observations of Larock concerning the reactivity of internal alkynes. If the formation of the pyrrolo[2,3-*g*]indazole substituted at the 8-position cannot be explained by the cyclization of an alkynyl intermediate, this is not the case for the preparation of 7-TMS-substituted compound **9**.

To get more insight into the mechanism of formation of compound **9**, alkynylindazole **8** was subjected to the reaction conditions used for the formation of compound **9** from indazole **6**. The formation of indole **9** from compound **8** was not observed in these conditions, neither in the presence of $PdCl_2$ in acetonitrile[20] nor CuI

in DMF.[21] Therefore, we suppose that a Larock annulation is most likely involved in the formation of compound **9**, and the effect of the silyl group had a strong influence on the regioselectivity issue of the reaction, which is opposite to the one we observed with the other terminal alkynes used in this study (Table 1, entries 2–5). Possibly, the observed unusual reactivity and regioselectivity of terminal alkynes may be due in part to an effect of the bulky electron-rich ligand XPhos used in this work.

We next investigated our reaction conditions to the palladium-catalyzed annulation of internal alkynes (Table 2). In a first approach, we tried terminal alkynes bearing a trimethylsilyl group, that were described by Larock to give regioselectively the indole product substituted by the silyl group at the 2-position (entries 1 and 2). With our conditions, the formation of only one regioisomer was observed but the reaction yielded only small quantities of products **21** and **22**. Nevertheless, despite the poor conversion of the reaction, the obtention of compounds **21** and **22** allowed us to check the regioselectivity issue of the annulation reaction. Thus, crude mixtures of compounds **6**/**21** and **6**/**22** were subjected to desilylation conditions in the presence of tetrabutylammonium fluoride. After chromatography, compounds **10** and **12** were isolated, showing that the silyl group was placed at the 7-position of the pyrrolo[2,3-*g*]indazole ring system.

**Table 2**
Indolization reaction with internal alkynes



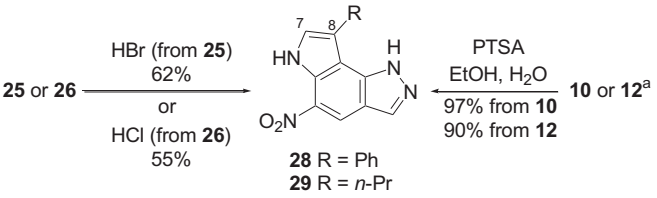

| Entry | $R^1$ | $R^2$ | Product | Yield |
|---|---|---|---|---|
| 1 | TMS | Ph | **21** | Not isolated[a] |
| 2 | TMS | *n*-Pr | **22** | Not isolated[a] |
| 3 | Et | Ph | **23** | 67% |
| | Ph | Et | **24** | 19% |
| 4 | $CO_2Et$ | Ph | **25** | 86% |
| 5 | $CO_2Me$ | *n*-Pr | **26** | 90% |
| 6 | $CO_2Et$ | Me | **27** | 94% |

[a] Inseparable mixture with starting material.

In the case of the other internal alkynes examined, the yields were found to be much higher. In the case of 1-phenylbut-1-yne (entry 3, Table 2), separable regioisomers **23** and **24** were obtained in 67% and 19% yields, respectively. Astonishingly, the major regioisomer was the one with the more sterically demanding group at the 3-position of the indole subunit, which is in accordance with our observation using terminal alkynes.

We also investigated internal alkynes bearing an ester function. To the best of our knowledge, the use of such acetylene derivatives for Larock indole annulation was rarely reported.[22] In our conditions, the reaction showed to be very efficient and highly regioselective as only one regioisomer was identified (compounds **25**–**27**, entries 4–6). Nevertheless, the regioselectivity was opposite to the one reported previously, the ester function being placed at the 2-position of the indole scaffold. The structure of compounds **25**–**27** was unambiguously confirmed by $^1H-^1H$ NOESY NMR experiments. Additionally, compounds **25** and **26** were decarboxylated to give deprotected pyrrolo[2,3-*g*]indazoles **28** and **29** in 62% and 55% yields, respectively (Scheme 3). These two compounds were identical to the deprotection products obtained by treatment of compounds **10** and **12** with PTSA in $EtOH/H_2O$.

As mentioned above, the use of a ligand such as XPhos may have an effect on the regioselectivity issue of the reaction with terminal alkynes. This should also be considered in the case of internal




**Scheme 3.** Decarboxylation of compounds **25** and **26**. Deprotection of compounds **10** and **12**. [a]A ~9:1 mixture of compounds **12**/**11** was used. Compound **29** was obtained as a mixture containing ~10% of the 7-propyl regioisomer.

alkynes. In addition, the high regioselectivity showed with propiolate ester derivatives may be due to the electronic effect of the ester function, and/or an interaction between the ester function and the amino group of the aniline moiety, affecting the regioselectivity of the alkyne insertion step. Nevertheless, considering the indolization reaction between an *o*-iodoaniline derivative and an alkyl 3-substituted propiolate, an alternative mechanistic pathway other than Larock indole annulation may be considered: (a) a 1,4-addition of the aniline nitrogen atom to the propiolate ester under basic condition, and (b) a palladium-catalyzed cyclization of the generated *N*-vinylaniline intermediate. In this case, the ester function would be found at the 3-position of the indole ring system. Actually, examples of such synthetic pathway are found in the literature[23] and might be involved in previous examples that described the access to indole derivatives bearing the ester function at the 3-position.[22] In our case, the observed regioselectivity (ester function at the 2-position of the indole ring system) showed that this mechanism is not applicable. This could be due to the low nucleophilicity of the aniline nitrogen of compound **6**, bearing an electron-withdrawing nitro group. Therefore, in our case, a Larock annulation is more likely.

## 3. Conclusion

In summary, we synthesized 1,6-dihydropyrrolo[2,3-*g*]indazole derivatives using a palladium-catalyzed annulation for the construction of the indole ring system. The annulation was performed by a Larock reaction in the presence of terminal or internal alkynes. Moreover, we observed a directing effect on regioselectivity mediated by the ester function of the alkyl 3-substituted propiolate derivatives used as internal alkynes.

## 4. Experimental section

### 4.1. General

Starting materials were obtained from commercial suppliers and used without further purification. Solvents were distilled prior to use. IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer ($\bar{\nu}$ in $cm^{-1}$). NMR spectra, performed on a Bruker AVANCE 400 ($^1H$: 400 MHz, $^{13}C$: 100 MHz), or a Bruker AVANCE 500 ($^1H$: 500 MHz, $^{13}C$: 126 MHz), are reported in parts per million using the solvent residual peak as an internal standard ($^1H$: DMSO-$d_6$, 2.50 ppm or $CDCl_3$, 7.26 ppm; $^{13}C$: DMSO-$d_6$, 39.52 ppm); for compounds **14**, **23**–**27**, $^{13}C$ NMR spectra were recorded in the presence of $CDCl_3$ in DMSO-$d_6$ (~1:5) to increase the solubility, using DMSO-$d_6$ as internal standard; the following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), doublet of doublet (dd), multiplet (m), broad signal (br s). High resolution mass spectra ($ESI^+$) were determined on a high-resolution Micro Q-Tof apparatus (CRMP, Université Blaise Pascal, Clermont-Ferrand, France). Chromatographic purifications were performed by flash silica gel Geduran SI 60 (Merck) 0.040–0.063 mm column chromatography. Reactions were monitored by TLC using fluorescent silica gel plates (60 $F_{254}$ from Merck).

Melting points were measured on a Reichert microscope and are uncorrected.

### 4.2. Procedures for preparation of compounds 4–8

*4.2.1. 5-Nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-amine (**4**), 6-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-amine (**5**), 7-iodo-5-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-amine (**6**), and 4-iodo-6-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-amine (**7**). Step A*: to a mixture of indazole derivative **3** (1.5 g, 5.1 mmol) and 10% Pd/C (600 mg, 0.56 mmol, 11 mol %) in methanol (45 mL) was added the 1,4-cyclohexadiene (5.1 mL, 54 mmol). The mixture was refluxed for 3 h and the catalyst was removed by filtration through a Celite pad, which was subsequently washed with methanol (50 mL). The filtrate was evaporated under reduced pressure and the residue was purified by flash chromatography (cyclohexane/EtOAc, 100:0 to 50:50) to give a mixture containing reduced products **4** and **5** (NMR ratio ~87:13) (1.2 g) as a red oil. The separation by chromatography of the two regioisomers was only practicable using small quantities. Therefore, the mixture was used for the next step without any further purification. Nevertheless, compounds **4** and **5** were separated by chromatography for characterization (cyclohexane/EtOAc, 100:0 to 0:100).

*Step B*: a solution of mixture from step A (500 mg) and iodine (2 g, 7.9 mmol) in DMSO (3 mL) was stirred at room temperature for 1 h. The solution was diluted in EtOAc (50 mL) and was washed with a saturated aqueous $Na_2S_2O_3$ solution (3×30 mL). The organic layer was dried over $MgSO_4$ and the residue obtained upon evaporation was purified by flash chromatography (cyclohexane/EtOAc, 100:0 to 0:100) to give **6** (472 mg, 1.22 mmol, 57%) as an orange powder and **7** (140 mg, 0.36 mmol, 17%) as a purple powder.

Compound **4**, yellow oil; IR (ATR): 3486, 3373, 1635, 1305, 1041 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): 1.51–1.63 (2H, m), 1.66–1.80 (1H, m), 1.90–2.06 (2H, m), 2.25–2.37 (1H, m), 3.62–3.71 (1H, m), 3.84–3.92 (1H, m), 5.58 (1H, d, $J$=9 Hz), 6.97 (1H, s), 7.00 (2H, br s), 8.09 (1H, s), 8.59 (1H, s); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): 22.0, 24.7, 28.6, 66.4 ($CH_2$), 84.3 (CH), 93.6, 121.1, 136.2 ($CH_{arom}$), 116.9, 130.8, 142.6, 144.1 ($C_{arom}$); HRMS ($ESI^+$) calcd for $C_{12}H_{14}N_4NaO_3$ $(M+Na)^+$ 285.0964, found 285.0975.

Compound **5**, red oil; IR (ATR): 3501, 3393, 1635, 1520, 1483, 1451, 1295 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): 1.49–1.64 (2H, m), 1.65–1.81 (1H, m), 1.91–2.06 (2H, m), 2.28–2.39 (1H, m), 3.72–3.80 (1H, m), 3.81–3.89 (1H, m), 5.87 (1H, dd, $J_1$=9.5 Hz, $J_2$=2.5 Hz), 6.55 (2H, br s), 7.26 (1H, s), 8.03 (1H, s), 8.43 (1H, s); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): 22.0, 24.8, 28.8, 66.3 ($CH_2$), 83.8 (CH), 106.0, 107.2, 132.1 ($CH_{arom}$), 129.7, 131.7, 134.0, 139.7 ($C_{arom}$); HRMS ($ESI^+$) calcd for $C_{12}H_{14}N_4NaO_3$ $(M+Na)^+$ 285.0964, found 285.0960.

Compound **6**, mp=126 °C; IR (ATR): 3480, 3371, 1623, 1299, 1266, 1078, 1040 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): 1.50–1.78 (3H, m), 1.97–2.07 (2H, m), 2.41–2.55 (1H, m), 3.76–3.93 (2H, m), 6.55 (1H, d, $J$=9.5 Hz), 7.00 (2H, br s), 8.16 (1H, s), 8.67 (1H, s); $^{13}C$ NMR (126 MHz, DMSO-$d_6$): 22.9, 24.6, 28.8, 66.0 ($CH_2$), 82.7 (CH), 121.8, 136.7 ($CH_{arom}$), 62.5, 118.0, 130.4, 143.0, 143.4 ($C_{arom}$); HRMS ($ESI^+$) calcd for $C_{12}H_{13}IN_4NaO_3$ $(M+Na)^+$ 410.9930, found 410.9914.

Compound **7**, mp=107–108 °C; IR (ATR): 3458, 3342, 1513, 1430, 1288, 1168, 1076, 1056, 1038 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): 1.52–1.61 (2H, m), 1.68–1.78 (1H, m), 1.93–2.05 (2H, m), 2.28–2.37 (1H, m), 3.74–3.81 (1H, m), 3.82–3.87 (1H, m), 5.94 (1H, dd, $J_1$=9.5 Hz, $J_2$=2.5 Hz), 6.27 (2H, br s), 7.86 (1H, s), 8.58 (1H, s); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): 21.9, 24.7, 28.7, 66.3 ($CH_2$), 84.1 (CH), 109.1, 135.1 ($CH_{arom}$), 74.6, 131.0, 133.5, 134.4, 138.1 ($C_{arom}$); HRMS ($ESI^+$) calcd for $C_{12}H_{13}IN_4NaO_3$ $(M+Na)^+$ 410.9930, found 410.9924.

*4.2.2. 5-Nitro-1-(tetrahydro-2H-pyran-2-yl)-7-(2-trimethylsilylethynyl)-1H-indazol-6-amine (**8**).* To a mixture of compound **6** (30 mg, 0.077 mmol), $Pd(PPh_3)_4$ (9 mg, 7.8 μmol), CuI (3 mg, 0.016 mmol) in acetonitrile (2 mL) were added DIEA (20 mg, 0.15 mmol), and trimethylsilylacetylene (15 mg, 0.15 mmol). The mixture was refluxed for 5 h, and then was evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/EtOAc, 100:0 to 0:100) to give **8** (14 mg, 0.039 mmol, 51%) as a yellow powder; mp=112–113 °C; IR (ATR): 1620, 1419, 1314, 1292, 1258, 1253, 1249, 1078, 1037 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): 0.35 (9H, s), 1.51–1.70 (3H, m), 1.96–2.09 (2H, m), 2.35–2.47 (1H, m), 3.63–3.72 (1H, m), 3.90–3.97 (1H, m), 6.41 (1H, dd, $J_1$=10.5 Hz, $J_2$=2 Hz), 7.01 (2H, br s), 8.21 (1H, s), 8.72 (1H, s); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): −0.1 ($3CH_3$), 22.8, 24.6, 28.8, 66.1 ($CH_2$), 83.3, 123.0, 137.6 (CH), 87.7, 96.6, 107.9, 116.4, 130.4, 140.9, 145.9 (C); HRMS ($ESI^+$) calcd for $C_{17}H_{22}N_4NaO_3Si$ $(M+Na)^+$ 381.1359, found 381.1350.

### 4.3. General procedure for preparation of compounds 9, 10, 12, 14, 23–27

To a mixture of compound **6** (50 mg, 0.13 mmol), $Pd(PPh_3)_4$ (15 mg, 0.013 mmol), XPhos (12.5 mg, 0.026 mmol), and $K_2CO_3$ (36 mg, 0.26 mmol) under inert atmosphere in THF (2 mL) was added the alkyne (0.39 mmol). The solution was refluxed for 16 h, and then was evaporated under reduced pressure. The residue was purified by flash chromatography ($CH_2Cl_2$/cyclohexane/EtOAc, 10:90:0 to 10:0:90) to give the title compounds.

*4.3.1. 5-Nitro-1-(tetrahydro-2H-pyran-2-yl)-7-(trimethylsilyl)-1,6-dihydropyrrolo[2,3-g]indazole (**9**).* Yellow powder, 91%; mp=127–128 °C; IR (ATR): 3416, 1630, 1584, 1525, 1470, 1401, 1341, 1329, 1281, 1248, 1191, 1132, 1084, 1076, 1043 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): 0.42 (9H, s), 1.58–1.69 (2H, m), 1.82–1.93 (1H, m), 2.05–2.14 (2H, m), 2.40–2.54 (1H, m), 3.82–3.88 (1H, m), 3.93–3.99 (1H, m), 6.06 (1H, dd, $J_1$=9.5 Hz, $J_2$=2 Hz), 7.15 (1H, d, $J$=2 Hz), 8.35 (1H, s), 8.64 (1H, s), 11.99 (1H, br s); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): −0.9 ($3CH_3$), 21.8, 24.7, 28.6, 66.3 ($CH_2$), 85.3 (CH), 110.8, 114.9, 136.9 ($CH_{arom}$), 113.2, 117.0, 129.8, 130.7, 136.0, 140.0 ($C_{arom}$); HRMS ($ESI^+$) calcd for $C_{17}H_{22}N_4NaO_3Si$ $(M+Na)^+$ 381.1359, found 381.1361.

*4.3.2. 5-Nitro-8-phenyl-1-(tetrahydro-2H-pyran-2-yl)-1,6-dihydropyrrolo[2,3-g]indazole (**10**).* Brown powder, 97%; mp=179–181 °C; IR (ATR): 3500–3250, 1616, 1488, 1405, 1378, 1319, 1283, 1207, 1090, 1043 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): 0.71–0.86 (1H, m), 1.12–1.34 (2H, m), 1.61–1.76 (2H, m), 2.18–2.31 (1H, m), 2.50–2.58 (1H, m), 3.52–3.60 (1H, m), 4.99 (1H, dd, $J_1$=10.5 Hz, $J_2$=2 Hz), 7.49 (1H, d, $J$=2.5 Hz), 7.40–7.66 (5H, m), 8.46 (1H, s), 8.71 (1H, s), 12.34 (1H, br s); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): 22.0, 24.2, 28.6, 66.8 ($CH_2$), 85.8 (CH), 115.0, 126.0, 127.6 (single peak) and 128.2–130.3 (br s, chemical shift range evaluated from $^1H$–$^{13}C$ HSQC experiment) (5C), 139.2 ($CH_{arom}$), 111.4, 117.7, 118.2, 127.1, 130.6, 136.5, 137.9 ($C_{arom}$); HRMS ($ESI^+$) calcd for $C_{20}H_{18}N_4NaO_3$ $(M+Na)^+$ 385.1277, found 385.1295.

*4.3.3. 5-Nitro-8-propyl-1-(tetrahydro-2H-pyran-2-yl)-1,6-dihydropyrrolo[2,3-g]indazole (**12**).* Orange powder, ~1:9 mixture of regioisomers **11** and **12**, 96%; $^1H$ NMR (500 MHz, DMSO-$d_6$), major regioisomer **12**: 1.09 (3H, t, $J$=7.5 Hz), 1.58–1.95 (5H, m), 1.97–2.03 (1H, m), 2.07–2.15 (1H, m), 2.58–2.67 (1H, m), 2.97–3.12 (2H, m), 3.69–3.76 (1H, m), 3.92–3.98 (1H, m), 6.07 (1H, dd, $J_1$=9.5 Hz, $J_2$=2 Hz), 7.29 (1H, d, $J$=2.5 Hz), 8.25 (1H, s), 8.59 (1H, s), 11.91 (1H, br s). HRMS ($ESI^+$) calcd for $C_{17}H_{20}N_4NaO_3$ $(M+Na)^+$ 351.1433, found 351.1450.

*4.3.4. 8-Diethoxymethyl-5-nitro-1-(tetrahydro-2H-pyran-2-yl)-1,6-dihydropyrrolo[2,3-g]indazole (**14**).* Yellow powder, 56%; mp=181–182 °C; IR (ATR): 3384, 1614, 1412, 1380, 1328 $cm^{-1}$; $^1H$

NMR (500 MHz, DMSO-$d_6$): 1.06 (3H, t, $J$=7 Hz), 1.23 (3H, t, $J$=7 Hz), 1.57–1.64 (2H, m), 1.67–1.78 (1H, m), 1.93–1.99 (1H, m), 2.07–2.14 (1H, m), 2.51–2.60 (1H, m), 3.35–3.43 (1H, m), 3.46–3.54 (1H, m), 3.57–3.65 (1H, m), 3.78–3.90 (3H, m), 6.02 (1H, s), 6.77 (1H, br d, $J$=7.5 Hz), 7.59 (1H, d, $J$=2.5 Hz), 8.41 (1H, s), 8.66 (1H, s), 12.19 (1H, br s); $^{13}$C NMR (100 MHz, DMSO-$d_6$+$CDCl_3$): 14.9, 15.0 ($CH_3$), 22.3, 24.8, 29.7, 57.7, 62.4, 65.9 ($CH_2$), 83.3, 97.2 (CH), 114.8, 126.7, 137.8 ($CH_{arom}$), 109.7, 114.1, 118.0, 127.6, 130.2, 136.9 ($C_{arom}$); HRMS ($ESI^+$) calcd for $C_{19}H_{24}N_4NaO_5$ $(M+Na)^+$ 411.1644, found 411.1634.

*4.3.5. 7-Ethyl-5-nitro-8-phenyl-1-(tetrahydro-2H-pyran-2-yl)-1,6-dihydropyrrolo[2,3-g]indazole (**23**), and 8-ethyl-5-nitro-7-phenyl-1-(tetrahydro-2H-pyran-2-yl)-1,6-dihydropyrrolo[2,3-g]indazole (**24**).* Compound **23**, black powder, 67%; mp=127–128 °C; IR (ATR): 3372, 1615, 1492, 1401, 1315, 1276, 1261 $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): 0.70–0.84 (1H, m), 1.14 (3H, t, $J$=7.5 Hz), 1.11–1.32 (2H, m), 1.49–1.57 (1H, m), 1.64–1.72 (1H, m), 2.15–2.28 (1H, m), 2.56–2.79 (3H, m), 3.53–3.60 (1H, m), 4.74 (1H, d, $J$=10 Hz), 7.34–7.39 (1H, m), 7.50–7.58 (3H, m), 7.60–7.66 (1H, m), 8.41 (1H, s), 8.61 (1H, s), 12.09 (1H, br s); $^{13}$C NMR (100 MHz, DMSO-$d_6$+$CDCl_3$): 15.2 ($CH_3$), 18.9, 21.9, 24.2, 28.7, 66.6 ($CH_2$), 85.4 (CH), 113.4, 127.7, 128.8, 129.1, 130.3, 130.9, 138.8 ($CH_{arom}$), 112.5, 113.3, 118.2, 125.9, 130.2, 136.6, 137.1, 140.8 ($C_{arom}$); HRMS ($ESI^+$) calcd for $C_{22}H_{23}N_4O_3$ $(M+H)^+$ 391.1770, found 391.1773.

Compound **24**, brown powder, 19%; mp=120–121 °C; IR (ATR): 3384, 1605, 1493, 1396, 1326, 1316, 1081, 1044 $cm^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): 1.27 (3H, t, $J$=7.5 Hz), 1.57–1.77 (3H, m), 2.02–2.08 (1H, m), 2.08–2.16 (1H, m), 2.58–2.68 (1H, m), 2.96–3.11 (2H, m), 3.65–3.73 (1H, m), 3.90–3.97 (1H, m), 6.08 (1H, dd, $J_1$=9.5 Hz, $J_2$=2 Hz), 7.46 (1H, t, $J$=7 Hz), 7.53 (2H, t, $J$=7.5 Hz), 7.59 (2H, d, $J$=7.5 Hz), 8.42 (1H, s), 8.61 (1H, s), 11.70 (1H, br s); $^{13}$C NMR (126 MHz, DMSO-$d_6$+$CDCl_3$): 17.0 ($CH_3$), 18.7, 22.5, 24.6, 29.9, 66.5 ($CH_2$), 85.2 (CH), 114.3, 128.1, 128.2 (2C), 129.6 (2C), 138.2 ($CH_{arom}$), 112.9, 114.7, 118.0, 127.0, 130.4, 131.9, 136.5, 137.5 ($C_{arom}$); HRMS ($ESI^+$) calcd for $C_{22}H_{23}N_4O_3$ $(M+H)^+$ 391.1770, found 391.1777.

*4.3.6. Ethyl 5-nitro-8-phenyl-1-(tetrahydro-2H-pyran-2-yl)-1,6-dihydropyrrolo[2,3-g]indazole-7-carboxylate (**25**).* Yellow powder, 86%; mp=151–152 °C; IR (ATR): 3453, 1698, 1400, 1316, 1300, 1261, 1241 $cm^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): 0.76–0.87 (1H, m), 1.03 (3H, t, $J$=7 Hz), 1.14–1.32 (2H, m), 1.47–1.53 (1H, m), 1.64–1.71 (1H, m), 2.16–2.25 (1H, m), 2.67–2.73 (1H, m), 3.55–3.60 (1H, m), 4.07–4.19 (2H, m), 4.58 (1H, d, $J$=10 Hz), 7.41 (1H, d, $J$=7.5 Hz), 7.51–7.63 (4H, m), 8.49 (1H, s), 8.88 (1H, s), 11.26 (1H, br s); $^{13}$C NMR (100 MHz, DMSO-$d_6$+$CDCl_3$): 13.4 ($CH_3$), 21.6, 24.0, 28.7, 60.5, 66.5 ($CH_2$), 85.4 (CH), 118.9, 128.18, 128.25, 128.33, 129.7, 130.6, 139.2 ($CH_{arom}$), 112.7, 118.5, 122.5, 124.7, 127.3, 130.0, 135.0, 137.5 ($C_{arom}$), 159.9 (C=O); HRMS ($ESI^+$) calcd for $C_{23}H_{23}N_4O_5$ $(M+H)^+$ 435.1668, found 435.1689.

*4.3.7. Methyl 5-nitro-8-propyl-1-(tetrahydro-2H-pyran-2-yl)-1,6-dihydropyrrolo[2,3-g]indazole-7-carboxylate (**26**).* Yellow powder, 90%; mp=135–136 °C; IR (ATR): 3431, 1707, 1398, 1319, 1232, 1218, 1082, 1042 $cm^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): 1.06 (3H, t, $J$=7.5 Hz), 1.56–1.83 (5H, m), 2.07–2.17 (2H, m), 2.56–2.65 (1H, m), 3.09–3.17 (1H, m), 3.45–3.53 (1H, m), 3.70–3.77 (1H, m), 3.89–3.94 (1H, m), 3.95 (3H, s), 6.83 (1H, dd, $J_1$=9 Hz, $J_2$=2.5 Hz), 8.51 (1H, s), 8.86 (1H, s), 11.13 (1H, br s); $^{13}$C NMR (100 MHz, DMSO-$d_6$+$CDCl_3$): 13.6, 51.9 ($CH_3$), 22.1, 24.4, 24.8, 26.8, 29.6, 66.0 ($CH_2$), 85.0 (CH), 119.0, 138.5 ($CH_{arom}$), 112.7, 118.4, 123.5, 124.5, 127.7, 130.0, 137.7 ($C_{arom}$), 160.6 (C=O); HRMS ($ESI^+$) calcd for $C_{19}H_{22}N_4NaO_5$ $(M+Na)^+$ 409.1488, found 409.1488.

*4.3.8. Ethyl 8-methyl-5-nitro-1-(tetrahydro-2H-pyran-2-yl)-1,6-dihydropyrrolo[2,3-g]indazole-7-carboxylate (**27**).* Yellow powder, 94%; mp=135–136 °C; IR (ATR): 3447, 1707, 1309, 1232, 1083, 1040 $cm^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): 1.39 (3H, t, $J$=7 Hz), 1.57–1.64 (2H, m), 1.71–1.82 (1H, m), 1.96–2.02 (1H, m), 2.04–2.11 (1H, m), 2.53–2.62 (1H, m), 3.01 (3H, s), 3.68–3.75 (1H, m), 3.86–3.92 (1H, m), 4.41 (2H, q, $J$=7 Hz), 6.18 (1H, dd, $J_1$=9 Hz, $J_2$=2 Hz), 8.48 (1H, s), 8.85 (1H, s), 10.98 (1H, br s); $^{13}$C NMR (100 MHz, DMSO-$d_6$+$CDCl_3$): 11.6, 14.1 ($CH_3$), 22.0, 24.4, 29.5, 60.7, 65.9 ($CH_2$), 84.8 (CH), 118.8, 138.1 ($CH_{arom}$), 113.7, 118.0, 119.3, 123.7, 127.6, 129.9, 137.8 ($C_{arom}$), 160.5 (C=O); HRMS ($ESI^+$) calcd for $C_{18}H_{21}N_4O_5$ $(M+H)^+$ 373.1512, found 373.1507.

### 4.4. Procedures for preparation of compounds 28 and 29

Procedure A: a solution of indazoles **25** or **26** in concentrated hydrochloric or hydrobromic acid, respectively, was refluxed for 2 h. A saturated aqueous $NaHCO_3$ solution (20 mL) was added and the solution was extracted with EtOAc (2×20 mL). The combined organic fractions were dried over $MgSO_4$ and then evaporated. Flash chromatography (cyclohexane/EtOAc, 100:0 to 0:100) provided the title compounds.

Procedure B: to a solution of indazoles **10** or **12** (~1:9 **11**/**12** mixture) in ethanol and water was added PTSA monohydrate (20 mol %). The mixture was refluxed for 16 h. A saturated aqueous $NaHCO_3$ solution (10 mL) was added and the solution was extracted with EtOAc (2×30 mL). The combined organic layers were dried over $MgSO_4$ and then evaporated. Flash chromatography (cyclohexane/EtOAc, 100:0 to 0:100) provided the title compounds.

*4.4.1. 5-Nitro-8-phenyl-1,6-dihydropyrrolo[2,3-g]indazole (**28**).* Procedure A: compound **25** (10 mg, 0.023 mmol), concentrated HCl (1 mL); **28** (4 mg, 0.014 mmol, 62%).

Procedure B: compound **10** (130 mg, 0.36 mmol), ethanol (5 mL), water (3 mL); **28** (97 mg, 0.35 mmol, 97%).

Yellow powder; mp=193–194 °C; IR (ATR): 3446, 3268, 1632, 1480, 1317, 1282, 1234, 1076 $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): 7.35 (1H, t, $J$=7.5 Hz), 7.50 (2H, t, $J$=7.5 Hz), 7.60 (1H, d, $J$=2.5 Hz), 7.76 (2H, br s), 8.50 (1H, br s), 8.73 (1H, s), 12.22 (1H, br s), 13.08 (1H, br s); $^1$H NMR (400 MHz, $CDCl_3$): 7.44–7.50 (2H, m), 7.58 (2H, t, $J$=7.5 Hz), 7.66 (2H, d, $J$=7 Hz), 8.28 (1H, s), 8.69 (1H, s), 10.25–10.47 (2H, br s); $^{13}$C NMR: due to the low solubility of compound **28** in organic solvents, its $^{13}$C NMR spectrum could not be recorded; HRMS ($ESI^+$) calcd for $C_{15}H_{11}N_4O_2$ $(M+H)^+$ 279.0882, found 279.0893.

*4.4.2. 5-Nitro-8-propyl-1,6-dihydropyrrolo[2,3-g]indazole (**29**).* Procedure A: compound **26** (20 mg, 0.052 mmol), concentrated HBr (2 mL); **29** (7 mg, 0.029 mmol, 55%).

Procedure B: mixture of compounds **11** and **12** (~1:9) (84 mg, 0.26 mmol), ethanol (3 mL), water (3 mL); compound **29** (56 mg, 0.23 mmol, 90%) was obtained as a mixture containing ~10% of the 7-propyl regioisomer.

Orange powder; mp >250 °C; IR (ATR): 3450–3300, 3300–3050, 1635, 1454, 1324, 1292, 1201, 1086 $cm^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): 0.98 (3H, t, $J$=7.5 Hz), 1.68 (2H, quint, $J$=7.5 Hz), 2.96 (2H, t, $J$=7.5 Hz), 7.23 (1H, s), 8.37 (1H, s), 8.61 (1H, s), 11.78 (1H, br s), 13.62 (1H, br s); $^{13}$C NMR (126 MHz, DMSO-$d_6$): 13.5 ($CH_3$), 23.7, 27.2 ($CH_2$), 114.2, 123.0, 137.4 ($CH_{arom}$), 112.3, 116.2, 116.4, 125.7, 130.2, 136.6 ($C_{arom}$); HRMS ($ESI^+$) calcd for $C_{12}H_{13}N_4O_2$ $(M+H)^+$ 245.1039, found 245.1033.

## Acknowledgements

We are grateful for the financial support of ANR (ANR-08-JCJC-0131-CSD 3). The authors thank Bertrand Légeret for mass spectra analysis.

## References and notes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19. Characteristic $^{1}H$ NMR signals ($\delta$ in ppm) that enabled the determination of the regioisomer ratio. Compounds **15** and **16** (500 MHz, DMSO-$d_6$), **15**: 6.05 (1H, m), 7.06 (1H, s), 8.37 (1H, s), 8.64 (1H, s), 12.15 (1H, br s); **16**: 6.56 (1H, dd, $J_1$=8.5 Hz, $J_2$=2.5 Hz), 7.67 (1H, s), 8.45 (1H, s), 8.70 (1H, s), 12.22 (1H, br s). Compounds **17** and **18** (400 MHz, DMSO-$d_6$), major regioisomer: 6.66 (1H, d, $J$=8.5 Hz), 7.52 (1H, s), 8.43 (1H, s), 8.66 (1H, s), 12.05 (1H, br s); minor regioisomer: 6.01 (1H, d, $J$=9 Hz), 6.94 (1H, s), 8.35 (1H, s), 8.59 (1H, s), 11.85 (1H, br s). Compounds **19** and **20** (400 MHz, CDCl3), major regioisomer: 5.95 (1H, d, $J$=8.5 Hz), 8.20 (1H, s); minor regioisomer: 6.21 (1H, d, $J$=8.5 Hz), 8.29 (1H, s).
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