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

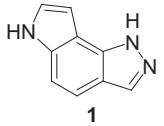
The palladium-catalyzed annulation of internal alkynes proved to be a useful method to access 2,3-disubstituted indole derivatives. Thus, Larock indolization led efficiently to this ring system from 2-iodoaniline derivatives by internal alkyne insertion to an arylpalladium bond and subsequent cyclization 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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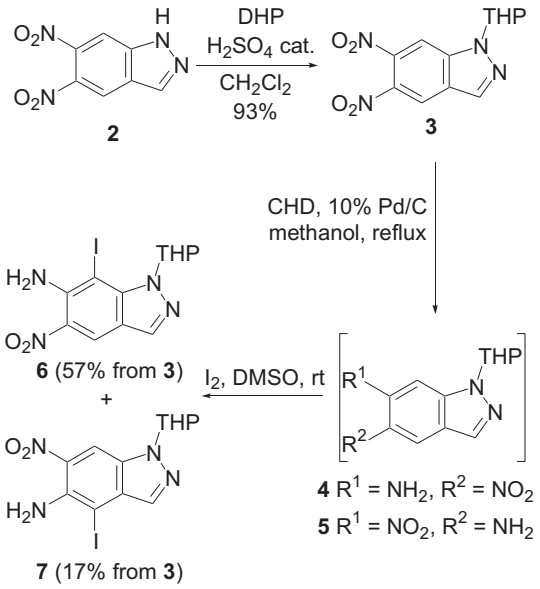
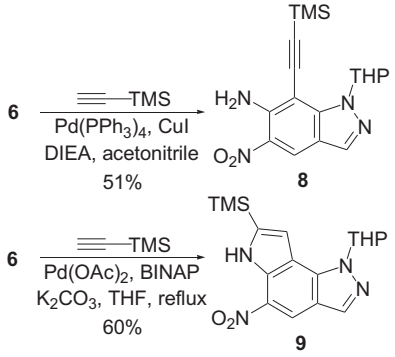
doi:10.1016/j.tet.2011.07.029



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).

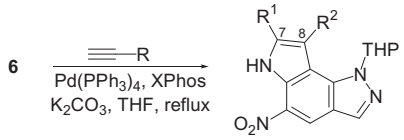


Scheme 2. Synthesis compounds **8** and **9**.

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