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Sonogashira cross-coupling reaction of 3-iodoindazoles with various terminal alkynes: a mild and flexible strategy to design 2-aza tryptamines

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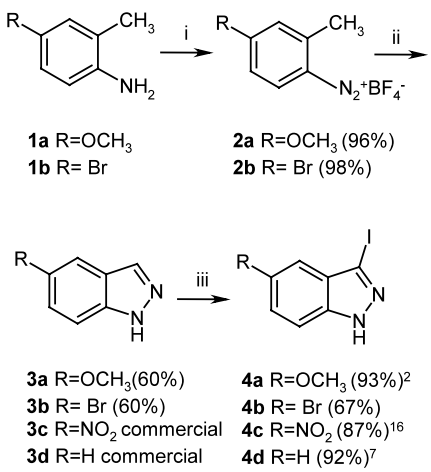
Abstract—This paper describes a Sonogashira-type cross-coupling reaction of 3-iodoindazoles with various terminal alkynes as a general route to 3-alkynylindazoles. The coupling reaction is illustrated by the preparation of new indazolylpropiolic or propargylic derivatives. Scope and limitation of the method are outlined.

1. Introduction

Although indazole is the 2-azabioisostere of indole, very few publications are devoted to its chemistry in comparison with the indole. However, some indazole derivatives such as 7-NI,[1] 7-MI[2] (nitric oxide synthase inhibitors), YC 1 (guanylyl cyclase activator),[3] granisetron (5HT-3 receptor antagonist),[4] lonidamine (cytotoxic modulator)[5] or SE063 (HIV protease inhibitor)[6] are already considered as leads in medicinal chemistry. Aiming at studying mild and flexible strategies to design new indazole librairies, we recently published a very efficient Suzuki cross-coupling reaction leading to 3-arylindazoles[7] and a general and versatile pathway leading to 3-indazolylpropionic acid and derivatives via a Heck cross-coupling reaction of 3-iodoindazoles.[8] We also depicted that these reactions could be carried out selectively or together with *N*-arylations.[9]

As a part of our research program on the design of 2-aza bioisosteres of tryptamine, serotonin or melatonin, we planned to develop an efficient method for the synthesis of 3-alkynylindazoles. An indepth survey of the literature did not show such a study. For this purpose, we applied the most straightforward methods for the preparation of arylalkynes which is the palladium-catalyzed coupling of terminal alkynes with arylhalides described for the first time by Sonogashira et al. in 1975.[10]



Scheme 1. *Reagents and conditions*: (i) (1) HBF_4 aq. 50%, (2) $NaNO_2$ aq, 0°C; (ii) AcOK, 18-crown-6, $CHCl_3$, rt; (iii) I_2, KOH, DMF, rt.

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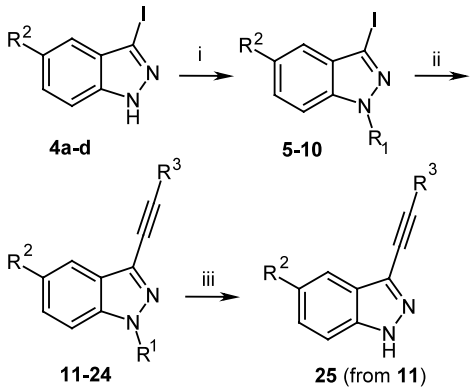


Scheme 2. (i) TosCl, *t*-BuOK, THF, 7 h (85%) or $(Boc)_2O$, DMAP, TEA, CH_3CN, 3 h (88%); (ii) H—≡—R^3, $PdCl_2(PPh_3)_2$ (5 mol%), Et_3N, CuI, DMF, rt; (iii) MeONa, MeOH, rt.

2. Results and discussion

Most of the syntheses of the indazole derivatives reported in the literature proceed from benzene precursors, in which the pyrazole moiety was generated by ring closure starting from isatines, phenylhydrazines or *o*-toluidines.[11–13] Amongst these reactions, we found that the most common ones proceed by a phase transfer catalyzed reaction from *o*-methylbenzendiazonium tetrafluoroborates.[2,14] 5-Methoxyindazole **3a** and 5-bromoindazole **3b** were prepared in this way (Scheme 1). 3-Iodoindazoles **4a**–**d** bearing either electron-withdrawing or electron-donating substituents in position 5 were obtained by direct iodination of indazoles **3** modifying[7] the method previously described by Bocchi[15] (Scheme 1).

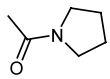
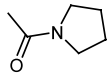
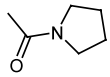
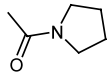
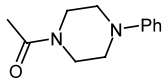
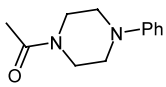
As for our precedent work concerning the Heck cross-coupling reaction of 3-iodoindazoles with acrylic derivatives,[8] our preliminary attempts of coupling reaction from **4d** with 1-propioloylpyrrolidine according to the classical conditions of Sonogashira coupling demonstrated the need for protecting the nitrogen group in the N-1 position. Indeed, without protection there is no coupling in position 3 and the product of the reaction is mainly the adduct on N-1. On the other hand, when the same reaction was conducted from the *N*-protected-3-iodoindazoles **5**–**10**, the reactions generally ran quickly with high yield affording the indazolylpropiolamides **11**–**23** (Scheme 2).

These good results have to be compared with the lack of reactivity of the methyl propiolate, which in our hands and various conditions never gave the desired methylindazolyl propiolate. Indeed, it has been documented that terminal acetylenes containing an electron-withdrawing group directly attached to the ethynyl carbon atom react poorly with aryl halides.[17,18] This obvious difference of reactivity between ester and carboxamide acetylene derivatives during the cross coupling reactions seems to have not been well documented and we found only one description of Sonogashira reactions using propiolamide itself and *N*-methylpropiolamide.[18] The lack of a more detailed investigation on the cross coupling capability of electron deficient propiolic amides is undoubtedly due to the fact that these alkynes are often difficult to prepare and to purify. For our own part we chose to adapt a method firstly described by Papanastassiou[19] (DCC in CH_2Cl_2) and details concerning our method will be published elsewhere. In our hands the methods using mixed anhydride or acid chloride as intermediate were able to produce sufficiently pure carboxamides.

To go further, we finally studied this cross coupling reaction of 3-iodoindazoles with *N*,*N*-dimethyl- or *N*-tosyl propargylamines. As expected, the results were very good with quantitative couplings to give the indazolyl propargylamines **16**–**23**. The result was the same for the *N*-tosylpentynylamine to give **24**.

All these results are summarized in Table 1.

Table 1. Sonogashira cross-coupling reactions of 3-iodoindazoles

Entry	3-II	R^1	R^2	R^3	Product	Yield(%)
1	**5**	Boc	H	CO_2Me		----
2	**4d**	H	H			O
3	**5**	Boc	H		**11**	80
4	**7**	Boc	OCH_3		**12**	92
5	**10**	Boc	NO_2		**13**	72
6	**5**	Boc	H		**14**	88
7	**6**	Tos	H		**15**	65
8	**4d**	H	H		**16**	<5
9	**5**	Boc	H		**17**	95
10	**7**	Boc	OCH_3		**18**	98
11	**8**	Tos	OCH_3		**19**	65
12	**10**	Boc	NO_2		**20**	98
13	**9**	Boc	Br		**21**	98
14	**5**	Boc	H	$CH_2NH(Tos)$	**22**	95
15	**9**	Boc	Br	$CH_2NH(Tos)$	**23**	91
16	**5**	Boc	H	$(CH_2)_3NH(Tos)$	**24**	99

All reactions were carried out according to the general procedure.[20]

We have to point out that the influence of the nature of the substituents of the indazole on the benzene moiety seems to have a very poor influence on the course of the coupling reaction. Importantly, when this substituent is a bromine atom, as for **9**, cross couplings conducted at room temperature are totally selective in position 3 without any double cross coupling products. However, a second palladium-catalyzed cross coupling reaction seems to be possible under more drastic conditions—reactions that are currently investigated by us. Another general comment concerning the *N*-protected group could be as follows: Boc protection seems to be better than Tos one. Indeed, we observed that Boc protecting group was stable during this coupling reaction in contrast to Tos, which was partially cleaved as it can be noted by comparison of the results in entries 6–7 or 10–11. Finally, the Boc group can be easily removed by treatment with sodium methoxide in methanol at room temperature.

In conclusion, the Sonogashira cross-coupling reaction of 3-iodoindazoles with various propiolic or propargylic derivatives appears as a general method to prepare new building blocks of interest in medicinal chemistry, as for example new aza analogues of tryptamine derivatives. Biological studies concerning these compounds are currently in progress.

Acknowledgements

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20. General procedure for the preparation of *N*-protected 3-alkynylindazoles. 3-Iodoindazole (2.0 mmol), $Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (10 mol%), alkyne (2.4 mmol), TEA (20 mL) and DMF (10 mL) were stirred under argon overnight. The mixture was then poured into water and extracted three times with dichloromethane (3×30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated on reduced pressure. The crude product was purified by column chromatography (silica gel).