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Heck cross-coupling reaction of 3-iodoindazoles with methyl acrylate: a mild and flexible strategy to design 2-azatryptamines

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Abstract

In order to design 2-azabioisosteres of tryptamine, serotonin or melatonin, the conditions of the Heck coupling reaction of 3-iodoindazoles with methyl acrylate are studied. This reaction authorizes the synthesis of 3-indazolylpropenoates as key intermediates to prepare 3-indazolylpropionic acids and 3-indazolylethylamines. The flexible synthetic strategy allows molecular diversity. © 2000 Elsevier Science Ltd. All rights reserved.

Although indazole is an azabioisostere of indole, very few publications are devoted to its chemistry in comparison with the indole. However, some indazole derivatives such as 7-NI (nitric oxide synthase inhibitor),[1] YC-1 (guanylyl cyclase activator),[2] granisetron (5HT-3 receptor antagonist),[3] lonidamine (cytotoxic modulator)[4] or SE063 (HIV protease inhibitor),[5] are already considered as leads in medicinal chemistry. Aimed at studying mild and flexible strategies to design new indazole libraries, we recently published a very efficient Suzuki cross-coupling reaction leading to 3-arylindazoles.[6] We report here a general and versatile pathway leading to 3-indazolylpropionic acid (3-(1*H*-indazol-3-yl)-propionic acid) and 3-indazolylethylamine (2-(1*H*-indazol-3-yl)-ethylamine) via a Heck cross-coupling reaction of 3-iodoindazoles with methyl acrylate in the presence of a catalytic amount of dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II) ($PdCl_2$(dppf)).

3-Iodoindazoles **2** are obtained by direct iodination of indazoles **1** modifying[6] the method previously described by Bocchi and Palli.[7]

Preliminary attempts of coupling reaction from 3-iodoindazoles **2** demonstrated the necessity of a protecting group in the N-1 position. When the cross-coupling reaction was conducted from unprotected indazoles **2**, it led only to the Michael adducts **12** without reaction at the 3 position

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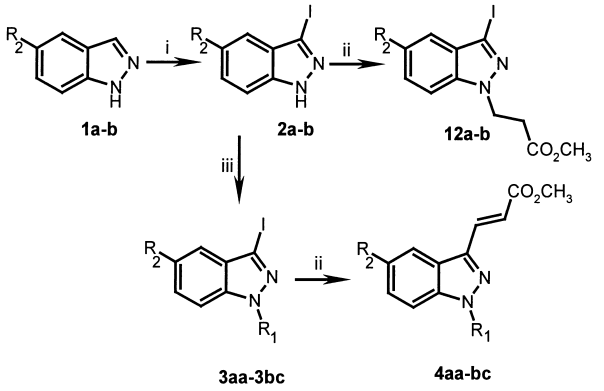
(Scheme 1). In contrast, when the same reaction was conducted from the *N*-protected-3-iodoindazoles **3**, the coupling reaction was very efficient affording the propenoates **4**.



Scheme 1. Heck cross-coupling reaction of 3-iodoindazoles with methyl acrylate. *Reagents and conditions*: (i) I_2, KOH, DMF, rt, 2 h (90%); (ii) methyl acrylate, $PdCl_2$(dppf), TEA, TBAI, DMF, 50°C, 2 h; (iii) $PhCH_2Br$ or TosCl, *t*-BuOK, THF, 8 h (85%) or $(Boc)_2O$, DMAP, TEA, CH_3CN, 3 h (88%)

It must be pointed out that the Boc-protecting group was stable during this coupling reaction in contrast to Tos which was partially cleaved. This is why Boc should be preferred as the labile-protecting group. On the other hand, $PdCl_2$(dppf) catalyst[8] in a mixture of DMF:H_2O containing TEA and tetrabutylammonium iodide (TBAI) (Method A) was found to be superior[9] to the traditional Heck-coupling catalyst $Pd(OAc)_2/PPh_3$[10] (Method B) (Table 1).

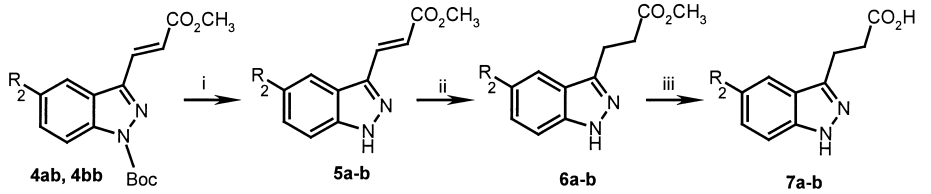
Table 1
Efficiency of various conditions on the formation of 3-indazolylpropenoates **4**

	R_1	R_2	Conditions	**4** (%)
2a	H	H	A	0
3aa	Bn	H	A	58
3ab	Boc	H	A	62
3ab	Boc	H	B	**77**
2b	H	OCH_3	A	0
3bc	Tos	OCH_3	A	20*
3ba	Bn	OCH_3	A	31
3bb	Boc	OCH_3	A	58
3bb	Boc	OCH_3	B	**75**

* with partial cleavage of Tos
A: $Pd(OAc)_2$, PPh_3, TEA, dioxane, 80°C
B: $PdCl_2$(dppf), TEA, TBAI, DMF, 50°C

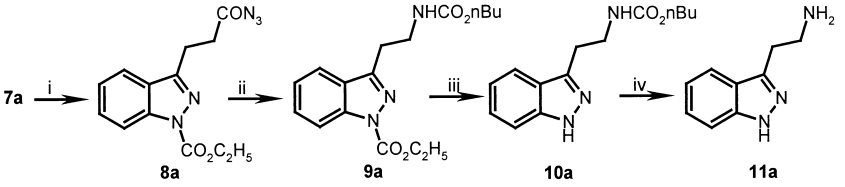
Several attempts of reduction of the ethylenic double bond of **4** with sodium borohydride in the presence of nickel(II) chloride hexahydrate[11] showed that a preliminary cleavage of the Boc group was necessary to prevent the formation of a mixture of protected and unprotected compounds

during this reaction. So, prior to the reduction, the cleavage was easily realized with sodium methoxide in methanol at room temperature to give the unprotected methyl propenoates **5** which then were reduced to give the methyl 3-indazolylpropionates **6**. Saponification of the ester at room temperature in an aqueous sodium hydroxide solution gave the 3-indazolylpropionic acids **7** (Scheme 2) in about 46% yield from the parent indazoles.



Scheme 2. Synthesis of 3-indazolylpropionic acids **7**. *Reagents and conditions*: (i) MeONa, MeOH, rt, 1 h (100%); (ii) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, MeOH, rt, 6 h (85%); (iii) NaOH 6N, THF, rt, 6 h (95%)

Furthermore, in order to obtain 3-indazolylethylamine derivatives, we studied the conditions of the Curtius rearrangement of **7a**. At this stage the formation of the carbonyl azide via the mixed anhydride needed the protection of N-1. Fortunately, we found that the N-1 protection and the formation of the carbonyl azide could be achieved in one step, by adjusting the reaction conditions. Thus, when the formation of the mixed anhydride intermediate was achieved with 2 equivalents of ethyl chloroformate in the presence of 2 equivalents of triethylamine, the reaction gave quantitatively the protection of N-1 with the ethoxycarbonyl group. Treatment of this non-isolated intermediate with 1 equivalent of sodium azide gave quantitatively the stable N-1-protected propionyl azide **8a** (Scheme 3).



Scheme 3. Synthesis of 3-indazolylethylamines. *Reagents and conditions*: (i) $ClCO_2Et$ (2 equiv.), TEA (2 equiv.), acetone, 0°C, NaN_3 (>95%); (ii) *n*-butanol, 115°C, 10 min (>95%); (iii) MeONa, MeOH, rt (95%); (iv) KOH 6N, DME, reflux, 12 h (>95%)

Due to the relative stability of this carbonyl azide, the Curtius rearrangement was conducted at 115°C in boiling *n*-butanol, leading quantitatively to the bis-protected 3-indazolylethylamine **9a**. Then the two protecting groups were cleaved selectively. Treatment of **9a** with sodium methoxide in methanol at room temperature produced the cleavage of the ethoxycarbonyl group to give the monoprotected butyloxycarbonylethylamine **10a**.[12] Finally, deprotection of **10a** was achieved in a mixture of aqueous potassium hydroxide solution and DME at reflux overnight. The four-step sequence of the rearrangement of the carboxylic acid **7a** into amine **11a** is quasi-quantitative.

In conclusion, the Heck cross-coupling reaction of 3-iodoindazoles with methyl acrylate authorizes, in mild conditions, the design of new libraries of 2-aza analogues of indole derivatives

with potent interest in medicinal chemistry. At each step the reaction conditions were adjusted to be automated and to reach molecular diversity. Application of this strategy to the preparation of serotonin and melatonin analogues will be published elsewhere with the biological results.

Acknowledgements

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9. Procedure for the preparation of 3-(2-methoxycarbonyl-vinyl)-indazol-1-carboxylic acid *tert*-butyl ester **4ab** (Method B): *N*-Boc-3-iodoindazole **3ab** (1 g, 2.9 mmol) was dissolved in a mixture of DMF:H_2O:TEA (25:4:4 mL). To this solution were added methyl acrylate (2.6 mL, 10 equiv.), {$PdCl_2$(dppf)} (0.42g, 0.58 mmol, 0.2 equiv.) and tetrabutylammonium iodide (2.14 g, 2 equiv.). The resulting mixture was heated at 50°C for 2 h. After cooling to room temperature, the excess of methyl acrylate was evaporated. H_2O (300 mL) was added. The precipitate was filtered and washed with H_2O. The solid was extracted with Et_2O (3×100 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by chromatography (silica gel, EtOAc:cyclohexane, 1:3) giving **4ab** as a yellow solid (0.68 g, 77%); mp 176°C. ^{1}H NMR ($CDCl_3$) δ 8.12 (d, 1H, J = 8.5 Hz), 7.92 (d, 1H, J = 16.5 Hz), 7.84 (d, 1H, J = 8 Hz), 7.50 (t, 1H, J = 7 Hz), 7.32 (t, 1H, J = 7 Hz), 6.88 (d, 1H, J = 16.5 Hz), 3.80 (s, 3H), 1.68 (s, 9H).
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