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New practical access to 2-azatryptophans and dehydro derivatives via the Wittig–Horner reaction

François Crestey, Valérie Collot,* Silvia Stiebing, Jean-François Lohier, Jana Sopkova-de Oliveira Santos and Sylvain Rault

Centre d'Etudes et de Recherche sur le Médicament de Normandie (CERMN), UPRES EA-3915, U.F.R. des Sciences Pharmaceutiques, Université de Caen Basse-Normandie 5, rue Vaubénard 14032 CAEN Cedex, France

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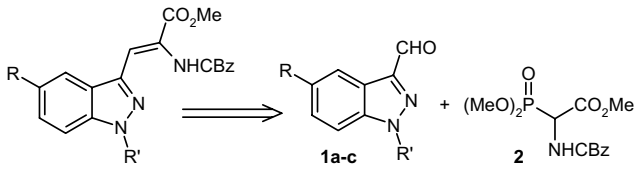
Abstract—The Wittig–Horner reaction of protected 3-formylindazoles **1** with (±)-*N*-(benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester **2** has been developed as a new practical synthesis of dehydro 2-azatryptophans and amino acid derivatives. The preparation of 5-bromo-3-formylindazole is discussed.

Our group has long been interested in the design and synthesis of new polyfunctionalized indazole libraries,[1] and particularly of 2-aza bioisosteres of tryptamine, serotonine or melatonine.[2]

Furthermore, we developed two new methodologies for the synthesis of 2-azatryptophans and dehydro derivatives by a nucleophilic substitution[3] and by a Heck cross-coupling reaction.[4] In order to obtain 2-azatryptophans and dehydro derivatives with more labile orthogonal protecting groups we decided to study the react- ivity of the protected 3-formylindazoles **1a**–**c** towards the (±)-*N*-(benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester **2** in the Wittig–Horner reaction (Scheme 1).



Scheme 1.

The results of our investigation of the latter reaction, which led to the development of a new practical synthesis of 2-azatryptophans and dehydro derivatives, are provided below.

To begin, we focused on the synthesis of 3-formylindazoles **3a**–**c**. In a survey of literature, we were surprised to find that very few methods have been reported for the synthesis of the 3-formylindazoles.[5]

Recently, we started to develop a new synthesis of 3-formylindazoles[6] by reduction of *N*-methoxy-*N*-methylamides (Weinreb amides) (R = H, OMe). Herein we have enlarged and applied this methodology to prepare 5-bromo derivatives from the corresponding isatine.

Unsubstituted carboxylic acid **5c** was commercially available, contrary to 5-bromo **5a** and 5-methoxy **5b** derivatives which were obtained by treatment of the corresponding isatines **4a**–**b** in a three-step procedure in very high yields as described in Scheme 2: cleavage with aqueous sodium hydroxide, diazotization with aqueous sodium nitrite in sulfuric acid, and finally reduction and cyclization of the intermediate diazonium salts with a cooled solution of tin(II) chloride dihydrate in hydrochloric acid.[7]

We found that the coupling reaction of **5a**–**c** with *N*,*O*-dimethyl-hydroxylamine hydrochloride, EDC,[8] and pyridine as base in THF furnished the Weinreb amides **6a**–**c** in 83, 68 and 84% yields, respectively. The reduction of

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* Corresponding author. Tel.: +33 2 31 93 64 58; fax: +33 2 31 93 11 88; e-mail: valerie.collot@unicaen.fr

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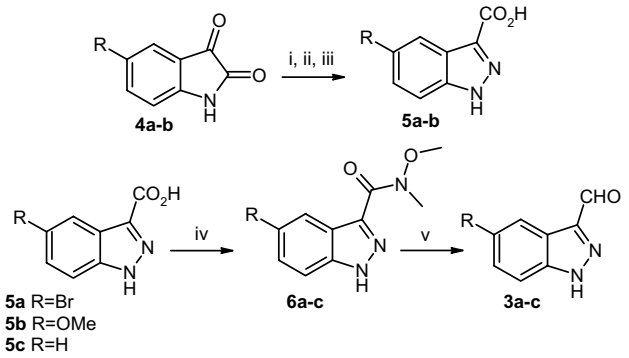


Scheme 2. Reagents and conditions: (i) NaOH aq (1.03 equiv), 20 min, 50 °C; (ii) $NaNO_2$ aq (1 equiv), H_2SO_4 concn, 1 h, 0 °C; (iii) $SnCl_2{\cdot}2H_2O$ (2.4 equiv), HCl concn, 16 h, rt, 98–100%; (iv) NH(OMe)Me·HCl (1.1 equiv), pyridine (2.2 equiv), THF, 1.5 h, 0 °C then EDC (2 equiv), pyridine (2 equiv), 12 h, rt, 68–84%; (v) $LiAlH_4$ (1.5 equiv), THF, 1 h at −15 °C then 12 h at rt, 10–76%.

Table 1. Synthesis of the 3-formylindazoles **3**

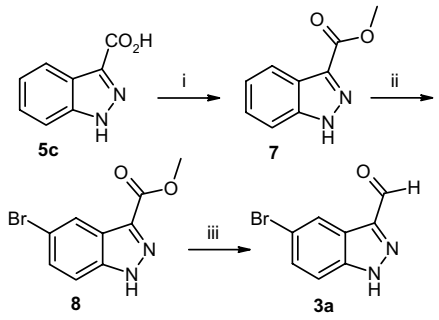
	5 (%)	**6** (%)	**3** (%)
R = Br (**a**)	100	83	10
R = OMe (**b**)	98	68	64
R = H (**c**)	Com.	84	76

Com.: commercial.

these amides was performed in THF with $LiAlH_4$ (1.5 equiv)[9] to afford aldehydes **3a**–**c** in 10, 64 and 76% yields, respectively (Scheme 2 and Table 1).

As a result of the low yield in the bromo series, we decided to modify our strategy to obtain aldehyde **3a**. First, we direct the bromination of 3-formylindazole **3c**, adapting a performed method that was described with indole by Bocchi and Palla[10] and Barili and coworkers,[11] with 1 equiv of Br_2 in DMF at 0 °C. Under these conditions, the desired brominated aldehyde was obtained in an unsatisfactory 18% yield. Finally, we found that aldehyde **3a** could be provided in a three-step pathway starting from the carboxylic acid **5c**. In the presence of a catalytic amount of sulfuric acid, under reflux conditions in methanol, ester **7** was isolated in 98% yield. Then, the bromination was performed with Br_2 in DMF at 0 °C to yield indazole **8** in 63%. Taking into account the reduction results reported by Schobert et al. on ferulic derivatives,[12] we started to reduce compound **8** with 3 equiv of Dibal–H. The reaction was monitored by TLC and after 1 h at −10 °C, 3 additional equivalents of Dibal–H were added. After 1 h at −10 °C and 12 h at room temperature, all the starting material was consumed, and the crude material was poured directly into a solution of ethyl acetate containing 10 equiv of manganese oxide. After 24 h at room temperature, 5-bromo-3-formylindazole **3a** was obtained in 86% yield as a white solid (Scheme 3).

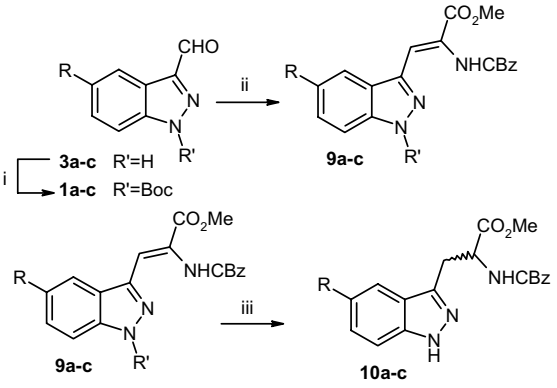
To perform the Wittig–Horner reaction,[13] we needed to protect indazoles **3a**–**c**. We chose the *tert*-butyloxycarbonyl (Boc) group which seemed to be the most appropriate and the reaction with $(Boc)_2O$ in the presence of



Scheme 3. Reagents and conditions: (i) MeOH, H_2SO_4 concn (cat.), 2 h, reflux conditions, 98%; (ii) Br_2 (1 equiv), DMF, 1 h at 0 °C then 3 h at rt, 63%; (iii) (1) Dibal–H (3 equiv), THF, 1 h, −10 °C then Dibal–H (3 equiv), THF, 1 h at −10 °C then 12 h at rt; (2) MnO_2 (10 equiv), EtOAc, 24 h, rt, 86%.

triethylamine (TEA) and a catalytic amount of dimethylaminopyridine (DMAP) in dichloromethane, provided protected compounds **1a**–**c** in 94, 96 and 100% yields, respectively (Scheme 4 and Table 2).

Phosphonate **2** has already been used in the Wittig–Horner reaction. Several examples have been described where the use of methanol or dichloromethane as solvent, and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU), *t*-BuOK or tetramethylguanidine (TMG) as base, yielded the dehydroamino acid with *Z*-configuration as a major product.[14] Several conditions were tried on our system in order to optimize the reaction. First, we decided to use indazole **1c**, 1.2 equiv of TMG and 1.1 equiv of phosphonate **2** in dichloromethane at room temperature, conditions inspired by the synthesis of the 3-pyrr-



Scheme 4. Reagents and conditions: (i) $(Boc)_2O$ (2 equiv), TEA (1.1 equiv), DMAP (cat.), CH_2Cl_2, 1 h at 0 °C then 12 h at rt, 94–100%; (ii) phosphonate **2** (1.1 equiv), DBU (1.2 equiv), 1 h at −84 °C then 1 h to rt then 1 h at rt, 76–81%; (iii) $NaBH_4$ (5 equiv), $NiCl_2{\cdot}6H_2O$ (0.2 equiv), 1 h at 0 °C then 12 h at rt, 49–52%.

Table 2. Synthesis of the 2-azatryptophans and dehydro derivatives **9** and **10**

	1 (%)	**9** (%)	**10** (%)
R = Br (**a**)	94	76	49
R = OMe (**b**)	96	77	50
R = H (**c**)	100	81	52

olylalanine described by Beecher and Tirrell.[15] The desired dehydro compound **9c** was obtained in 43% yield. Next, the reaction was carried out under the same conditions with DBU as base, to afford indazole **9c** in 62% yield. As described recently by Bonauer et al.,[16] the role of the temperature in the Wittig–Horner reaction is very important. It was the reason why we tried to improve the result with a lower temperature. Thus, at −42 °C, we obtained the desired product in 66% yield, and finally the best conditions were found to be −84°C to furnish (*Z*) dehydro 2-azatryptophans **9a–c** in 76, 77 and 81% yields, respectively (Scheme 4 and Table 2).[17] The crystallization of indazole **9b** allowed us to record X-ray data and to confirm its structure.[18]

Next, our efforts focused on the reduction of the double bonds of dehydro compounds **9a–c**. Preliminary reduction attempts under hydrogen with palladium on activated carbon in methanol did not afford the desired products. Only the starting materials were recovered, most likely because of the slightly solubility of dehydro 2-azatryptophans in methanol. Fortunately, the reaction of sodium borohydride with indazoles **9a–c** in the presence of Ni(II) chloride hexahydrate[2a,15,19] reduced the double bonds, and simultaneously cleaved the Boc group to afford the azatryptophan derivatives **10a–c** in moderate yields (Scheme 4 and Table 2).[20]

To conclude we found a new means to access dehydro 2-azatryptophans obtained from a Wittig–Horner reaction between various protected 3-formylindazoles and the (±)-*N*-(benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester **2**. This method was easily scaled up for the synthesis of multi-gram amounts of dehydro amino acids. These compounds have been reduced to give the corresponding amino acid derivatives. This methodology allowed us to produce valuable new building blocks with potential applications in medicinal chemistry, particularly in the development of peptidomimetics. Further studies concerning the synthesis of new substituted derivatives are currently in progress.

Acknowledgement

We thank Dr. Christophe Philippo for helpful discussions.

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17. *Typical procedure for the Wittig–Horner reaction*: To a solution of phosphonate **2** (2.55 g, 7.7 mmol, 1.1 equiv) in freshly distilled dichloromethane (20 mL) under argon was added DBU (1.25 mL, 8.4 mmol, 1.2 equiv) at room temperature. The reaction mixture was cooled at −84 °C and a solution of protected 3-formylindazole **1c** (1.72 g, 7.0 mmol) in freshly distilled dichloromethane (15 mL) was added. The reaction mixture was allowed to react at this temperature over 1 h, then allowed to warm to room temperature and left to react for an additional hour. The organic layer was washed successively with HCl (0.5 M, 30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and evaporated in vacuo. The crude material was purified by column chromatography on silica gel (EtOAc–cyclohexane, 1:4) to give dehydro compound **9c** as a white solid (2.55 g, 81%). mp 135 °C. TLC $R_f = 0.4$ (EtOAc–cyclohexane, 1:4). IR (KBr): 3241, 2987, 1742, 1720, 1636, 1515, 1437, 1376, 1359, 1253, 1214, 1157, 1092, 968, 766, 755 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.59 (s, 9H), 3.89 (s, 3H), 5.20 (s, 2H), 6.65 (s, 1H), 7.32–7.40 (m, 6H), 7.57 (t, $J = 8.8$ Hz, 1H), 7.78 (d, $J = 7.6$ Hz, 1H), 8.22 (d, $J = 8.8$ Hz, 1H), 9.94 (br s, 1H).^{13}C NMR ($CDCl_3$) δ: 28.0, 52.8, 67.8, 84.8, 103.6, 114.7, 119.7, 124.1, 125.0, 128.3, 128.4, 128.5, 129.6, 133.7, 135.7, 139.8, 145.2, 148.8, 153.4, 165.1. MS (EI): m/z (%) = 451 (M^+, 4), 351 (18), 243 (41), 216 (17), 156 (22), 146 (45), 127 (15), 118 (10), 108 (31), 107 (26), 91 (100), 80 (39). Anal. Calcd for $C_{24}H_{25}N_3O_6$: C, 63.85; H, 5.58; N, 9.31. Found: C, 63.89; H, 5.77; N, 9.15.

18. CCDC-628745 (**9b**) contains the crystallographic data for this Letter. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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20. *Typical procedure of the reduction of the double bond*: To a solution of indazole **9c** (600 mg, 1.3 mmol) and $NiCl_2{\cdot}6H_2O$ (63 mg, 0.3 mmol, 0.2 equiv) in methanol (30 mL) was added $NaBH_4$ (251 mg, 6.7 mmol, 5 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, then 12 h at room temperature and concentrated in vacuo. The crude material was taken up in CH_2Cl_2 (20 mL), washed with brine (20 mL), and the organic layer was dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting product was purified by column chromatography on silica gel (EtOAc–cyclohexane, 1:2) to give amino acid **10c** as a colourless oil (242 mg, 52%). TLC $R_f = 0.35$ (EtOAc–cyclohexane, 1:2). IR (KBr): 3383, 2954, 1732, 1622, 1505, 1435, 1350, 1216, 1214, 1092, 1075, 908, 746, 698 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.46 (dd, $J = 14.9$ Hz and $J = 5.1$ Hz, 1H), 3.57 (dd, $J = 14.7$ Hz and $J = 7.6$ Hz, 1H), 3.62 (s, 3H), 4.88–4.92 (m, 1H), 5.04 (s, 2H), 6.33 (d, $J = 8.8$ Hz, 1H), 7.09 (t, $J = 7.6$ Hz, 1H), 7.22–7.32 (m, 6H), 7.40 (d, $J = 8.3$ Hz, 1H), 7.60 (d, $J = 8.3$ Hz, 1H). MS (EI): m/z (%) = 353 (M^+, 19), 218 (15), 203 (29), 202 (100), 186 (16), 158 (17), 132 (85), 131 (100), 92 (16), 91 (100). HRMS/EI Calcd for $C_{19}H_{19}N_3O_4$ $[M]^+$ 353.1375. Found: 353.1358.