AtlanChim Pharma

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LETTRE SCIENTIFIQUE

EDITO

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ATLANCHIM PHARMA & ATLANTIC BONE SCREEN
LES PARTENAIRES DE VOTRE R&D

ATLANCHIM PHARMA AND ATLANTIC BONE SCREEN YOUR R&D PARTNERS

Plusieurs mois se sont écoulés depuis le début de l'aventure AtlanChim Pharma et une réelle complémentarité des services ne cesse de se confirmer. En effet, les activités respectives des sociétés AtlanChim Pharma et Atlantic Bone Screen s'inscrivent ensemble dans une démarche d'accompagnement entièrement personnalisée des sociétés de l'industrie pharmaceutique, cosmétique, agrochimique et biotechnologique dans leurs phases de recherche et développement.

La société AtlanChim Pharma intervient dans la phase de recherche de molécules actives en proposant une expertise dans la synthèse chimique de molécules complexes à façon et la société Atlantic Bone Screen intervient dans la sélection des molécules synthétisées dans le domaine de la cancérologie et des pathologies ostéoarticulaires en proposant une large gamme de tests *in vitro* et *in vivo* pertinents.

A l'échelle humaine, cette dualité se révèle également par 4 binômes : 4 chimistes et 4 biologistes représentent la complémentarité des compétences humaines au sein du groupe (cf portrait d'une biologiste et d'un chimiste). Aussi, les chimistes d'AtlanChim Pharma illustrent, au même titre que le Professeur Jacques Lebreton et le Docteur André Guingant (Directeurs scientifiques de la société), la continuité du savoir-faire et de l'expertise de la société AtlanChim. Nos deux équipes forment ainsi votre partenaire privilégié dans l'optimisation, le développement et la validation de vos composés.

Elisabeth PORCHER
Votre lien privilégié vers la chimie et la biologie

Several months have gone by since the beginning of the adventure AtlanChim Pharma and a significant complementarity of services keeps on being confirmed. Indeed the respective activities of AtlanChim Pharma and Atlantic Bone Screen come within the personalized approach of supporting companies from pharmaceutical, cosmetics, agrochemical and biotech industry in their phases of research and development.

AtlanChim Pharma intervenes in the phase of active molecules research proposing an expertise in chemical synthesis of complex molecules. Atlantic Bone Screen plays its role in the selection of the molecules synthesized in the field of cancer research and bone and joint diseases proposing a wide range of relevant in vitro and in vivo tests.

On a human scale, this duality is also proven by 4 chemistry-biology teams: 4 chemists and 4 biologists represent the complementarity of human professional skills within the Group (cf description of a chemistry-biology team). Besides the chemists of AtlanChim Pharma, in the same way as Professor Jacques Lebreton and Doctor André Guingant (Scientific Directors), illustrate the continuity of AtlanChim know-how and expertise. Both teams represent your ideal partner in the optimization, development and validation of your compounds.

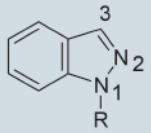
Elisabeth PORCHER
Your special link towards chemistry and biology

SOMMAIRE

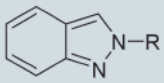
Preparation of substituted 1*H*- and 2*H*-indazole compounds

The indazole nucleus is a pharmaceutically important structure that constitutes the key subunit in many drugs with a broad range of pharmacological activities including, *inter alia*, anti-inflammatory, antimicrobial, antitumor, anti-HIV, antidepressant and antiplatelet activities. If the free energie values for the equilibrium between 1*H*-indazole and 2*H*-indazole (Figure 1, R=H) in aqueous phase was estimated[1] to be 2.3 kcal mol-1, so that the 1*H*-indazole form is highly predominent, the 1*H*-indazole and 2*H*-indazole structures may exist separately when R is a substituent different from H. Mainly because of their occurrence in drugs, there has been a sustained interest, in the past few years, for the discovery of new and efficient methods to prepare variously substituted 1*H*- and 2*H*-indazoles.

This Letter is intended to provide the reader with an overview of these novel synthetic methods. For the purpose of clarity, we will present the methods of preparation of substituted 1*H*- and 2*H*-indazole compounds separately.



1-R-1*H*-indazole



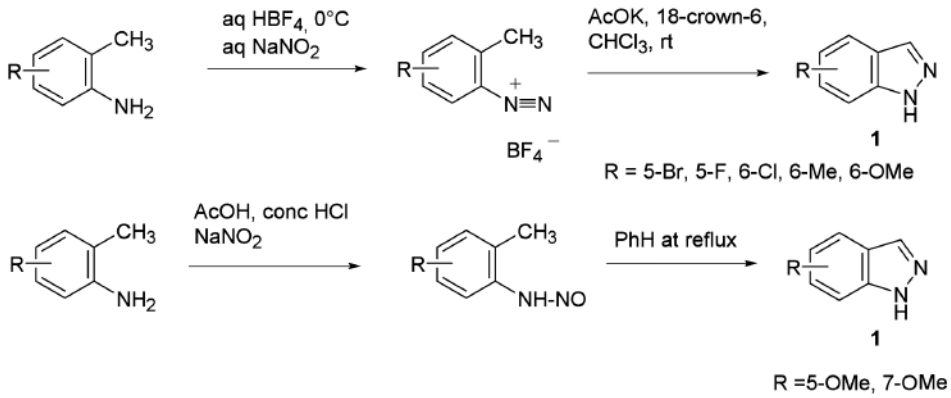
2-R-2*H*-indazole

A. Methods for the preparation of substituted 1*H*-indazole compounds

1. Creation of a C-N bond

Diazotation of an *o*-toluidine followed by capture of the generated diazonium salt is an old yet common way of accessing 1*H*-indazoles. This can be realized following two routes : the first and most common proceeds by a phase transfer-catalyzed reaction from *o*-methyl-benzendiazonium tetrafluoroborates (method of Bartsch and Yang);[2] the second takes place via *N*-nitroso derivatives (method of Kovach and Barnes).[3] These two procedures are well illustrated in the following example[4a] (Scheme 1). Several other examples are provided in refs [4b-i]

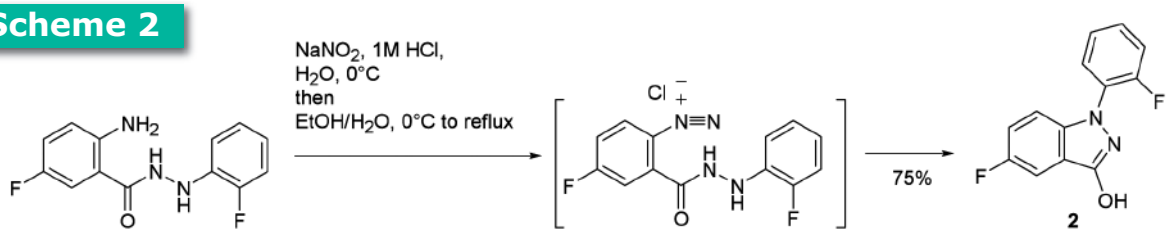
Scheme 1



[1] Catalan, J.; dePaz, J. L. G.; Elguero, J.; *J. Chem. Soc. Perkin Trans. 2*, **1996**, 57.
[2] Bartsch, R. A. ; Yang, I. W. *Heterocycl. Chem.* **1984**, *21*, 1063
[3] Kovach, E. G. ; Barnes, D. E. *J. Am. Chem. Soc.* **1954**, *76*, 1176.
[4] a) Schumann, P. ; Collot, V. ; Hommet, Y. ; Gsell, W. ; Dauphin, F. ; Sopkova, J. ; MacKenzie, E. T. ; Duval, D. ; Boulouard, M. ; Rault, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1153; b) Sun, J-H.; Teleha, C. A.; Yan, J-S.; Rodgers, J.D.; Nugiel, D. A. *J. Org. Chem.* **1997**, *62*, 5627; c) Vasudevan, A.; Souers, A. J.; Freeman, J. C.; Verzal, M. K.; Gao, J.; Mulhern, M. M.; Wodka, D.; Lynch, J. K.; Engstrom, K. M.; Wagaw, S. H.; Brodjian, S.; Dayton, B.; Falls, D. H.; Bush, E.; Brune, M.; Shapiro, R. D.; Marsh, K. C.; Hernandez, L. E.; Collins, C. A.; Kym, P. R. Bioorg. *Med. Chem. Lett.* **2005**, *15*, 5293 ; d) Drizin, I.; Gomtsyan, A.; Bayburt, E. K.; Schmidt, R. G.; Zheng, G. Z.; Perner, R. J.; DiDomenico, S.; Koenig, J. R.; Turner, S. C.; Jinkerson, T. K.; Brown, B. S.; Keddy, R. G.; McDonald, H. A.; Honore, P.; Wismer, C. T.; Marsh, K. C.; Wetter, J. M.; Polakowski, J. S.; Segreti, J. A.; Jarvis, M. F.; Faltynek, C. R.; Lee, C-H. Bioorg. *Med. Chem.* **2006**, *14*, 4740 ; e) Fraley, M. E.; Steen, J. T.; Brnardic, E. J.; Arrington, K. L.; Spencer, K. L.; Hanney, B. A.; Kim, Y.; Hartman, G. D.; Stirdivant, S. M.; Drakas, B. A.; Rickert, K.; Walsh, E.; Hamilton, K.; Buser, C. A.; Hardwick, J.; Tao, W.; Beck, S. C.; Mao, X.; Lobell, R. B.; Sepp-Lorenzino, L.; Yan, Y.; Ikuta, M.; Munshi, S. K.; Kuo, L. C.; Kreatsoulas, C. Bioorg. *Med. Chem. Lett.* **2006**, *16*, 6049 ; f) Iwakubo, M.; Takami, A.; Okada, Y.; Kawata, T.; Tagami, Y.; Ohashi, H.; Sato, M.; Sugiyama, T.; Fukushima, K.; Iijima, H. Bioorg. *Med. Chem.* **2007**, *15*, 350 ; g) Zhu, G-D.; Gong, J.; Gandhi, V. B.; Woods, K.; Luo, Y.; Liu, X.; Guan, R.; Klinghofer, V.; Johnson, E. F.; Stoll, V. S.; Mamo, M.; Li, Q.; Rosenberg, S. H.; Giranda, V. L. Bioorg. *Med. Chem.* **2007**, *15*, 2441; h) Boulouard, M. ; Schumann-Bard, P. ; Butt-Gueulle, S. ; Lohou, E. ; Stiebing, S. ; Collot, V. ; Rault, S. Bioorg. *Med. Chem. Lett.* **2007**, *17*, 3177; i) Shimada, I. ; Maeno, K. ; Kazuta, K-i. ; Kubota, H. ; Kimizuka, T. ; Kimura, Y. ; Hatanaka, K-i. ; Naitou, Y. ; Wanibuchi, F. ; Sakamoto, S. ; Tsukamoto, S-i. Bioorg. *Med. Chem.* **2008**, *16*, 1966.

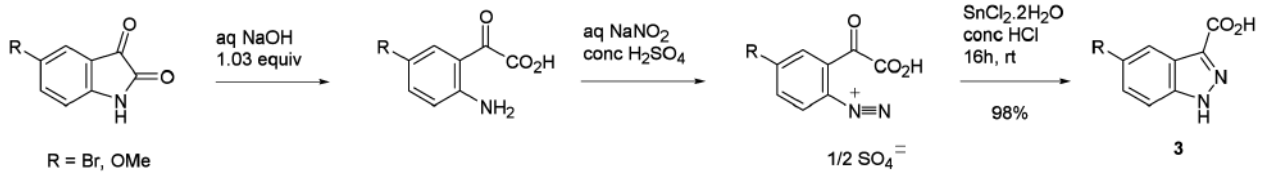
A different protocol proceeding *via* the intermediacy of a diazonium ion has also been reported. Thus, in the course of the preparation of an 1*H*-indazolone compound acting as norepiephedrine/serotonin reuptake inhibitor for the treatment of fibromyalgia, the construction of the 1*H*-indazolone core structure of precursor **2** has been accomplished via the decomposition of a diazonium ion and capture of the resulting aryl cation by an *ortho*-disposed hydrazide (Scheme 2).[5]

Scheme 2



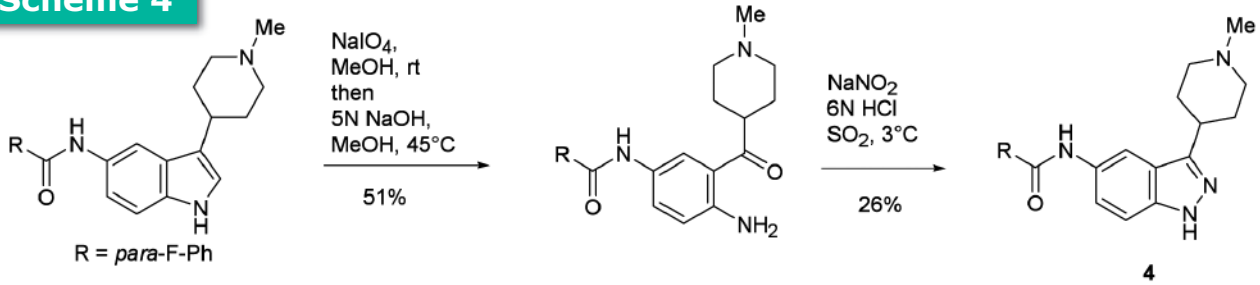
Reduction of a diazonium ion, or of a *N*-nitroso species, to the corresponding hydrazine and intramolecular reaction of the latter with an *ortho*-disposed carbonyl functionality is another way to reach 3-substituted-1*H*-indazoles. Following this protocol, 5-bromo and 5-methoxy-3-carboxy-1*H*-indazoles **3** have been prepared from properly substituted isatines (Scheme 3).[6a]

Scheme 3



Another example can be found in the work of Zhang et al.[6b] which, in the course of a study aimed at preparing bicyclic benzamides as novel 5-HT1F receptor agonists, have reported the preparation of 1*H*-indazole **4** (Scheme 4). It is worth noting that this example features an indole to indazole conversion[7] and reduction of the diazo intermediate with SO2. References 6[c-e] give additional examples.

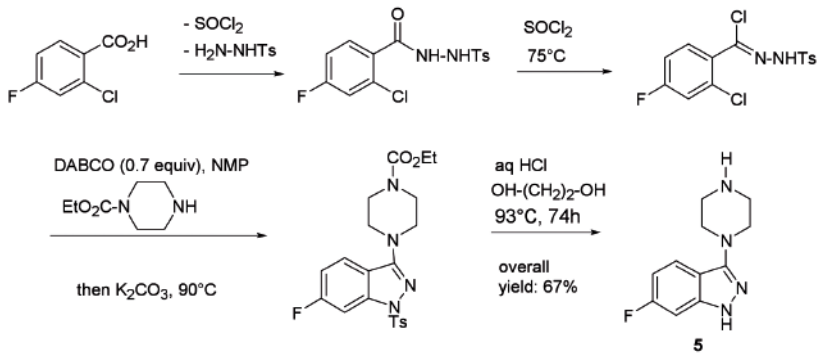
Scheme 4



[5] Magano, J.; Waldo, M.; Greene, D.; Nord, E. *Org. Process Res. Dev.* **2008**, *12*, 877.
[6a] Crestey, F.; Collot, V.; Stiebing, S.; Lohier, J-F.; Sopkova-de Oliveira Santos, J.; Rault, S. *Tetrahedron Lett.* **2007**, *48*, 2457;
[6b] Zhang, D.; Kohlman, D.; Krushinski, J.; Liang, S.; Ying, B-P.; Reilly, J. E.; Dinn, S. R.; Wainscott, D. B.; Nutter, S.; Gough, W.; Nelson, D. L. G.; Schaus, J. M.; Xu, Y-C. *Bioorg. Med. Chem. Lett.* 2004, *14*, 6011. c) Iwakubo, M.; Takami, A.; Okada, Y.; Kawata, T.; Tagami, Y.; Ohashi, H.; Sato, M.; Sugiyama, T.; Fukushima, K.; Iijima, H. *Bioorg. Med. Chem. 2007*, *15*, 350; d) Viña, D.; del Olmo, E.; López-Pérez, J.; San Feliciano, *A. Org. Lett.* **2007**, *9*, 525; e) Palazzo, G.; Corsi, G.; Baiocchi, L.; Silvestrini, B. *J. Med. Chem.* **1966**, *9*, 38.
[7] For previous work dealing with indole to indazole conversion, see : a) Bach, N. J. ; Kornfeld, E. C. ; Clemens, J. A. ; Smalstig, E. B. ; Frederikson, C. A. *J. Med. Chem.* **1980**, *23*, 492 ; b) Sasakura, K. ; Kawasaki, A. ; Sugasawa, T. *Synth. Commun.* **1988**, *18*, 259.

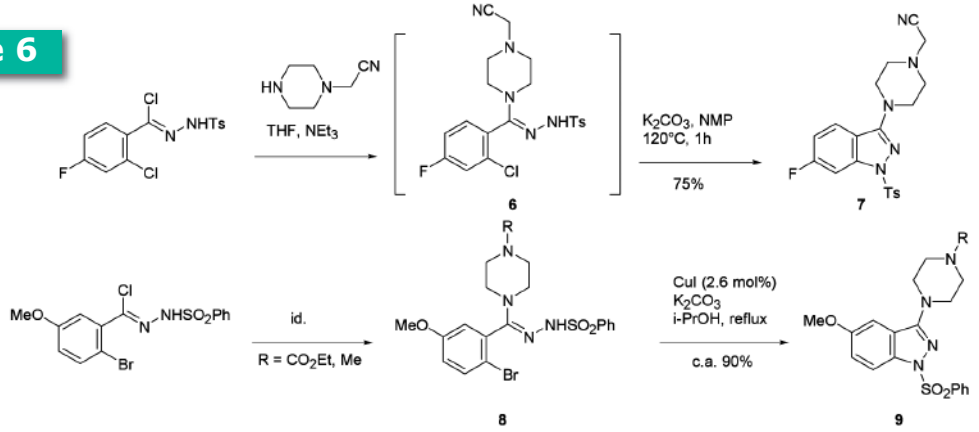
One common synthetic route to 1*H*-indazoles is the condensation of an arylketone, substituted in *ortho* by a leaving group (halogen, OMs), with hydrazine, followed by cyclization of the resulting hydrazone by simple heating or in the presence of a base. For example[8], a short and convenient synthesis of the 3-(1-piperazinyl)-1*H*-indazole derivative **5** has been successfully achieved. Compound **5** was obtained in 67% overall yield without the need for chromatographic purification (Scheme 5).

Scheme 5



Success in such an approach is greatly dependent on the phenyl ring electron density. This was clearly demonstrated in the following examples.[9a] Thus, if the cyclization of tosylhydrazone intermediate **6**, to give the corresponding 3-(1-piperazinyl)-1*H*-indazole **7**, could be easily accomplished by heating in NMP at 120°C in the presence of K_2CO_3 (see also Scheme 5), the much more electron-rich hydrazone intermediate **8** failed to cyclize, even at higher temperature (up to 160°C). However, the use of a catalytic amount of CuI promotes cyclization at reflux of isopropanol and in excellent yield (Scheme 6). Another example of CuI promoted cyclization of an arylhydrazone under microwave irradiation to give 1-aryl-1*H*-indazoles can be found in reference [9b].

Scheme 6



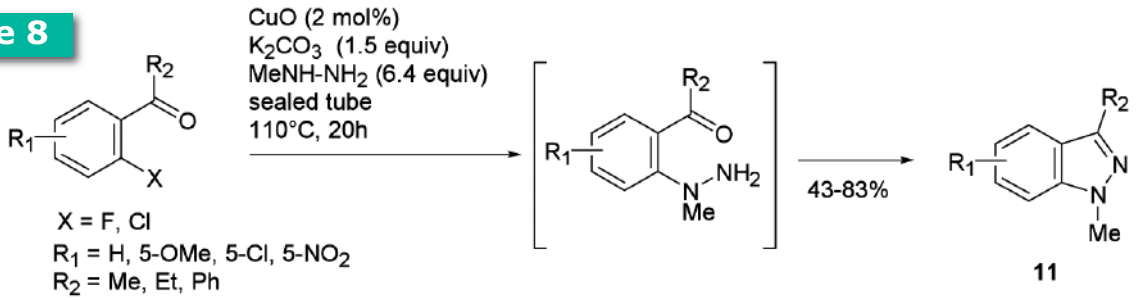
Based on the same strategy, the following example[10] depicts a slightly different route to 3-amino-1*H*-indazoles (Scheme 7). Three other examples of preparation of 3-amino-1*H*-indazoles can be found in references[11]; references[12] give additional examples of preparation of differently substituted 1*H*-indazoles.

Scheme 7

[8] Leroy, V.; Lee, G. E.; Lin, J.; Herman, S. H.; Lee, T. B. *Org. Process Res. Dev.* **2001**, *5*, 179.
[9] a) Watson, T. J.; Ayers, T. A, N. Shah, Wenstrup, D.; Webster, M.; Freund, D. *Org. Process Res. Dev.* **2003**, *7*, 521; b) Pabba, C.; Wang, H-J.; Mulligan, S. R.; Chen, Z-J.; Stark, T. M.; Gregg, B. T. *Tetrahedron Lett.* **2005**, *46*, 7553
[10] Burke, M. J. ; Trantow, B. M. *Tetrahedron Lett.* **2008**, *49*, 4579.
[11] a) Bauer, D.; Whittington, D. A.; Coxon, A.; Bready, J.; Harriman, S. P.; Patel, V. F.; Polverino, A.; harmange, J-C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4844; b) Yakaiah, T.; Lingaiah, B. P. V.; Narsaiah, B.; Shireesha, B.; Kumar, B. A.; Gururaj, S.; Parthasarathy, T.; Sridhar, B. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3445; c) Piccionello, A. P.; Pace, A.; Pibiri, I.; Buscemi, S.; Vivona, N. *Tetrahedron,* **2006**, *62*, 8792.
[12] a) Woods, K. W. ; Fisher, J. P. ; Clairborne, A. ; Li, T. ; Thomas, S. A. ; Zhu, G-D. ; Diebold, R. B. ; Liu, X. ; Shi, Y. ; Klinghofer, V. ; Han, E. K. ; Guan, R. ; Magnone, S. R. ; Johnson, E. F. ; Bouska, J. J. ; Olson, A. M. ; de Jong, R. ; Oltersdorf, T. ; Luo, Y. ; Rosenberg, S. H. ; Giranda, V. L.; Li, Q. *Bioorg. Med. Chem.* **2006**, *14*, 6832 ; b) Caron, S.; Vasquez, E. . *Org. Process Res. Dev.* **2001**, *5*, 587; c) Steffan, R. J.; Matelan, E.; Ashwell, M. A.; Moore, W. J.; Solvibile, W. R.; Trybulski, E.; Chadwick, C. C.; Chippari, S.; Kenney, T.; Eckert, A.; Borges-Marcucci, L.; Keith, J. C.; Xu, Z.; Mosyaz, L.; Harnish, D. C. J. *Med. Chem.* **2004**, *47*, 6435; d) Li, X.; Chu, S.; Feher, V. A.; Khalili, M.; Nie, Z.; Marosiak, S.; Nikulin, V.; Levin, J.; Sprankle, K. G.; Tedder, M. E.; Almassy, R.; Appelt, K.; Yager, K. M. J. *Med. Chem.* **2003**, *46*, 5663; e) Lee, Y-K.; Parks, D. J.; Lu, T.; Thieu, T. V.; Markotan, T.; Pan, W.; McComsey, D. F.; Milkiewicz, K. L.; Crysler, C. S.; Ninan, N.; Abad, M. C.; Giardino, E. C.; Maryanoff, B. E.; Damiano, B. P.; Player, M. R. J. *Med. Chem.* **2008**, *51*, 282;

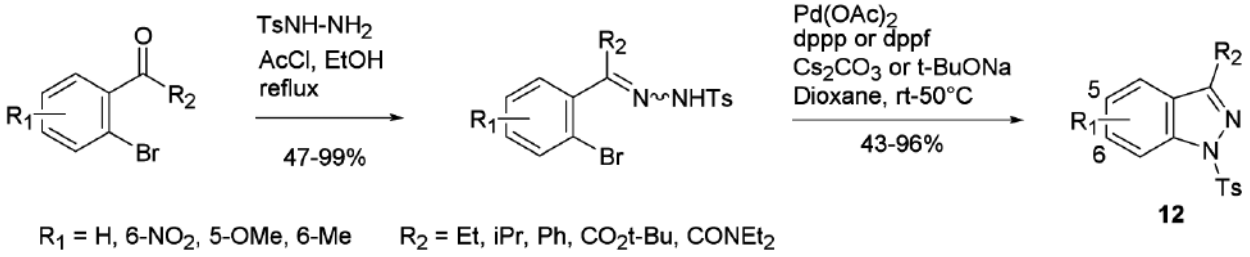
A regioselective one-step procedure to reach 1-alkyl and 1-phenyl-1*H*-indazoles has been recently reported based on the CuO-catalyzed reaction of *N*-methylhydrazine with 2-haloalkyl- or 2-halophenylketones[13]. Reactions were conducted in a sealed tube at 110°C and were interpreted as an Ullmann-type amination followed by cyclization. The same protocol could also be applied to 2-haloarylcarboxylic acids to give 1-methyl-3-hydroxy-1*H*-indazoles, although in quite lower yields. The reaction was also carried out with 2-fluorophenylmethylketone and differently substituted 1-hydrazines ($R_3NH\text{-}NH_2$, R_3 = *t*-Bu, Ph, $CH_2\text{-}CH_2OH$) to give differently 1-substituted-3-methyl-1*H*-indazoles in low to fair yields (Scheme 8).

Scheme 8



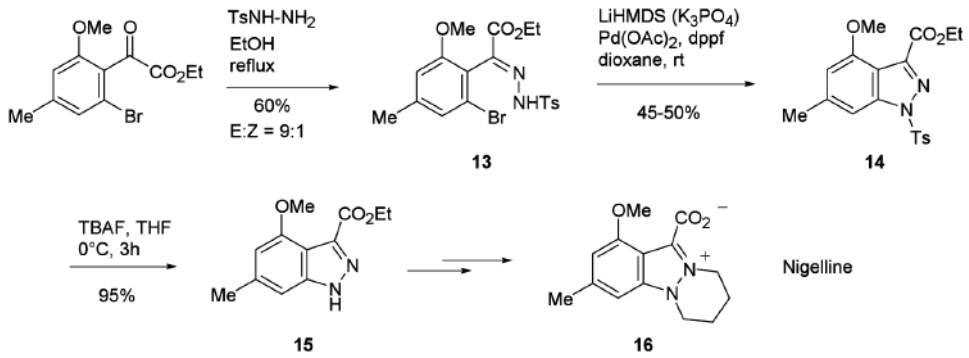
Several examples of preparation of 1-aryl-1*H*-indazoles *via* an intramolecular Pd-catalyzed amination reaction of tosylhydrazones have been reported. A recent example due to Inamoto et al.[14] is depicted in scheme 9.

Scheme 9



In the case of tosylhydrazone **13**, the catalyst system that gave good results in the precedent example induced the formation of 1*H*-indazole **14** in only poor yield. Instead, extensive degradation of tosylhydrazone **13** was observed, even at room temperature. After having tested several other conditions, it was finally discovered that the use of LiHMDS or K_3PO_4 as a base allowed the cyclization to proceed at room temperature in fair yield (45-50%). Indazole **14** was then *N*-deprotected to give **15**, the transformation of which to the natural alkaloid nigelline **16** could be achieved in two steps (Scheme 10). Other examples of palladium-induced formation of 1-aryl-1*H*-indazoles are listed in references [15].

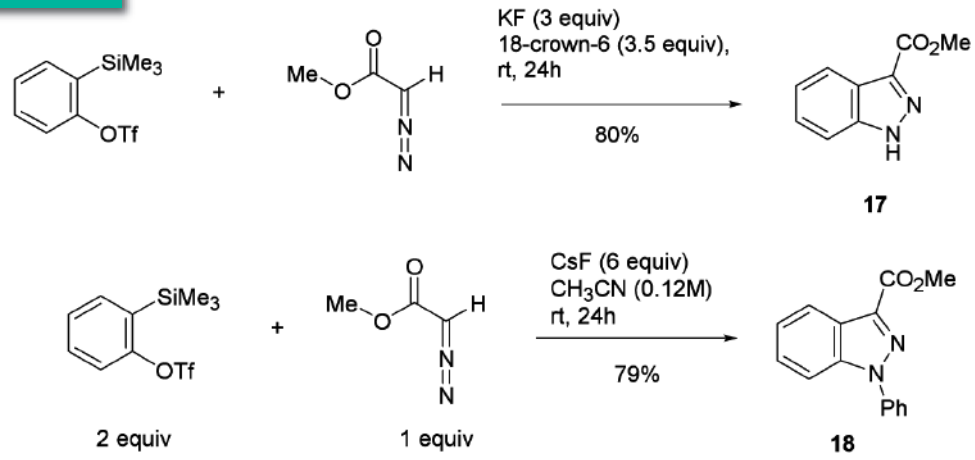
Scheme 10



[13] Viña, D.; del Olmo, E.; López-Pérez, J.; San Feliciano, A. *Org. Lett.* **2007**, *9*, 525.
[14] Inamoto, K.; Katsuno, M.; Takashi, Y.; Arai, Y.; Hiroya, K. ; Sakamoto, T. *Tetrahedron*, **2007**, *63*, 2695.
[15] a) Song, J. J.; Yee, N. K. Tetrahedron Lett. 2001, 42, 2937; b) Carbayo, A.; Cuevas, J. V.; Garcia-Herbosa, G. J. *Organomet. Chem.* **2002**, *658*, 1 ; c) Cho, C. S.; Lim, D. K.; Heo, N. H.; Kim, T-J.; Shim, S. C. *Chem. Commun.*, **2004**, *104*; d) Lebedev, A. Y.; Khartulyari, A. S.; Voskoboynikov, J. *Org.Chem.* **2005**, *70*, 596.

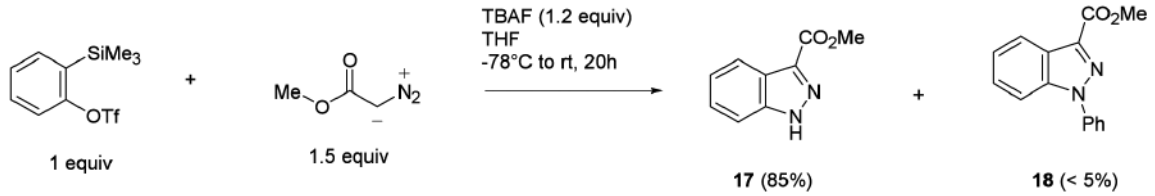
Recently, Yamamoto et al.[16] reported efficient procedure for synthesizing *N*-unsubstituted and 1-arylated-1*H*-indazoles via a [3+2] dipolar cycloaddition between arynes and diazomethane derivatives. Thus, treatment of *o*-TMS-phenyltriflate, as a benzyne precursor, and ethyldiazoacetate in THF at rt, in the presence of KF and a crown ether, afforded 3-ethoxycarbonyl-1*H*-indazole **17** in 80% yield. Substitution of the phenyl ring and use of several other diazo compounds (R-CH_2N_2 with R = t-BuO_2C, TMS, Ph) proved compatible with the reaction. In contrast, when *o*-TMS-phenyltriflate (2 equiv) was treated with ethyldiazoacetate in acetonitrile at rt in the presence of CsF in excess, 1-phenyl-3-ethoxycarbonyl-1*H*-indazole **18** was isolated in 79% yield (Scheme 11). Of course, compound **18** arised from arylation of intermediate **17** by the excess of *o*-TMS-phenyltriflate (→benzyne) in the medium. Variations in the structure of both cycloaddition reaction partners are possible.

Scheme 11



Almost at the same time, Larock and coll.[17] reported a more exhaustive study on similar work. The [3+2] dipolar cycloaddition between ethyldiazoacetate (1.5 equiv) and *o*-TMS-phenyl triflate (1 equiv) was accomplished in the presence of TBAF (1.2 equiv) as a fluoride source in THF at low temperature. In these conditions, 3-ethoxycarbonyl-1*H*-indazole **17** was formed in up to 85% yield along with small quantities (less than 5%) of 1-phenyl-3-ethoxycarbonyl-1*H*-indazole **18** (Scheme 12). Subsequent exploration of the scope and limitations of the reaction demonstrated that, by applying the same experimental conditions as above, a variety of benzyne precursors and monosubstituted diazomethane derivatives allowed the preparation of substituted 1*H*-indazoles in fair to good yields. Using an excess of benzyne precursor (2.4 equiv) led to 1-aryl substituted 1*H*-indazole compounds by capture of the excess aryne at nitrogen N1.

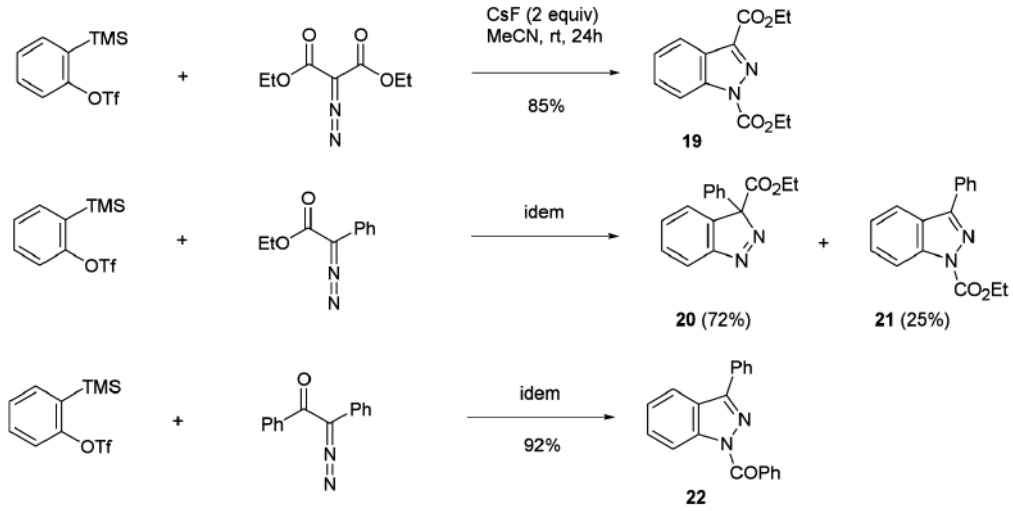
Scheme 12



[16] Jin, T.; Yamamoto, Y. *Angew. Chem.* **2007**, *119*, 3387.
[17] Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 219

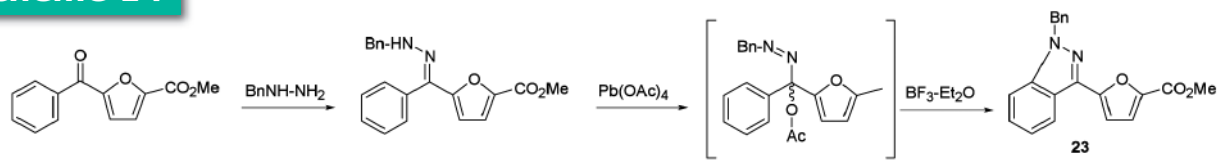
In a second part of their work, and following the pioneering work of Shechter and coll.[18], Larock and coll. focussed on the reaction of arynes with diazo substrates that do not have hydrogen on the diazo carbon. Thus, reaction of benzyne (from *o*-TMS-phenyl triflate) with diazo compounds having two carbonyl groups attached to the diazo carbon led quite generally to the product arising from [3+2] cycloaddition and 1,3-migration (carbon C3 to nitrogen N1) in good yield. When only one ester group was branched at the diazo carbon, the reaction led mainly, if not exclusively, to the product of cycloaddition. In contrast, when a ketone rather than an ester was attached at the diazo carbon, the product of cycloaddition-acyl migration was solely formed. Examples are shown in Scheme 13.

Scheme 13



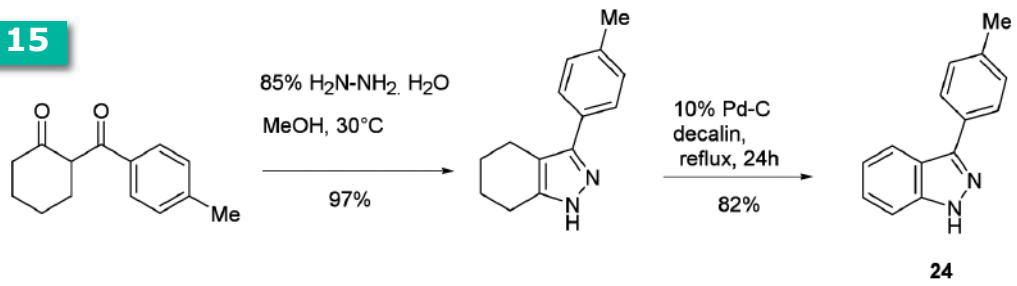
In the course of a work aimed at discovering novel antiplatelet agents derived from 1-benzyl-3-(5'-hydroxymethyl-2'-furyl) indazole, Lee et al.[19] reported an unusual synthesis of the 1*H*-indazole derivative **23** from a diaryketone. This ketone was first treated with benzylhydrazine to give the corresponding hydrazones (E + Z mixture). The latter mixture was then, under the action of lead tetraacetate, transformed to an azo compound intermediate which was subsequently cyclized to the desired 1*H*-indazole under Lewis acid activation (Scheme 14).

Scheme 14



In all above examples the 1*H*-indazoles were prepared from a substituted phenyl precursor. In relation with the search for novel compounds with anti-angiogenic activity, a recent paper[20] reported the preparation of 3-aryl-1*H*-indazoles by aromatization of 4,5,6,7-tetrahydro-1*H*-indazoles (Scheme 15).

Scheme 15



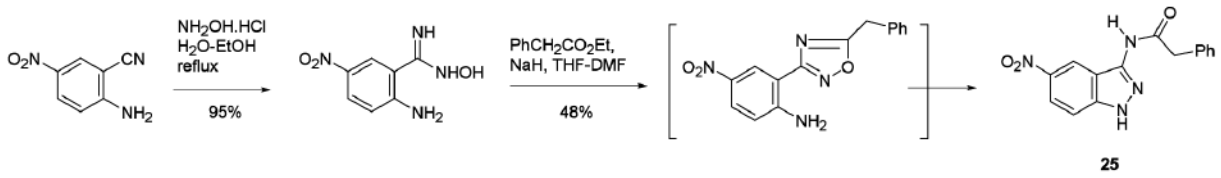
[18] a) Baum, G.; Bernard, R.; Shechter, H. J. *Am. Chem. Soc.* **1967**, *89*, 5307; Baum, G.; Shechter, H. J. *Org. Chem.* **1976**, *41*, 2120; b) Yamazaki, T.; Shechter, H. *Tetrahedron Lett.* **1972**, *13*, 4533; *ibid.* **1973**, *14*, 1417; Yamazaki, T.; c) Baum, G.; Shechter, H. *Tetrahedron Lett.* **1974**, *15*, 4421.

[19] Lee, F-Y.; Lien, J-C.; Huang, L-J.; Huang, T-M.; Tsai, S-C.; Teng, C-M.; Wu, C-C.; Cheng, F-C.; Kuo, S-C. J. *Med. Chem.;* **2001**, *44*, 3746.

2. Creation of the N_1-N_2 bond

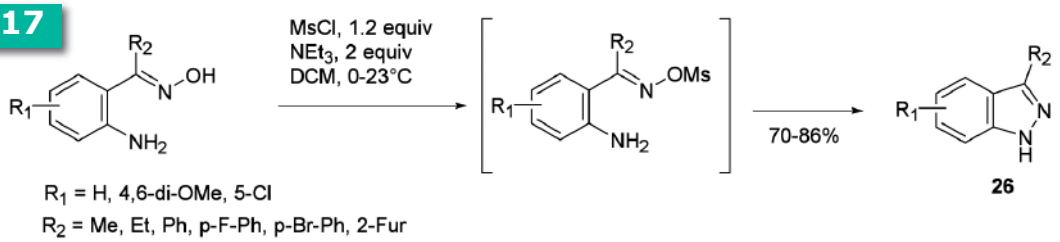
Not surprisingly, the methods of preparation of substituted 1*H*-indazoles via the formation of the N1-N2 bond are scarce in comparison to the methods that create a C-N bond. Few examples have been recently reported. In order to evaluate a series of 3,5-diamino-1*H*-indazoles as cyclin-dependent kinases (CDKs) inhibitors, Lee et al.[21] prepared the key intermediate 1*H*-indazole **25** from 2-amino-5-nitro-benzonitrile. Their approach features the transformation of the starting benzonitrile into a *N*-hydroxylamidine followed by its transformation to the target 1*H*-indazole via the formation of a 1,2,4-oxadiazole intermediate (Scheme 16).

Scheme 16

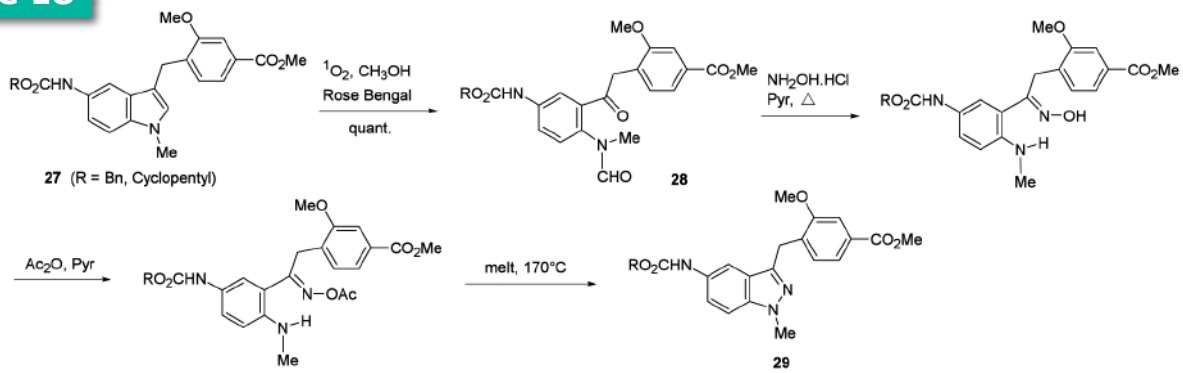


A protocol for the synthesis of 1*H*-indazoles from *o*-aminobenzoximes with creation of the N-N bond has been reported by Canceller et al.[22] It features the selective activation of the oxime group by reaction with a slight excess of methanesulfonyl chloride followed by cyclization to the 1*H*-indazoles by exposure to triethylamine at rt (Scheme 17). A similar strategy to reach 1*H*-indazoles had been reported previously by Matassa et al.[23] in a study directed at discovering potent and selective peptidoleukotriene antagonists, However, in the Matassa's report (Scheme 18) the synthesis of 1*H*-indazole **29** was achieved following an indole to indazole conversion. In practice, indole **27**, prepared in four steps from nitro-5-indole, was first submitted to the action of singlet oxygen to give the C2-C3 double bond oxidation product **28**. *(E)*-Oxime formation with concomitant removal of the formyl group, acetylation to give the corresponding oxime acetate then cyclization completed the synthesis of 1*H*-indazole **29**.

Scheme 17



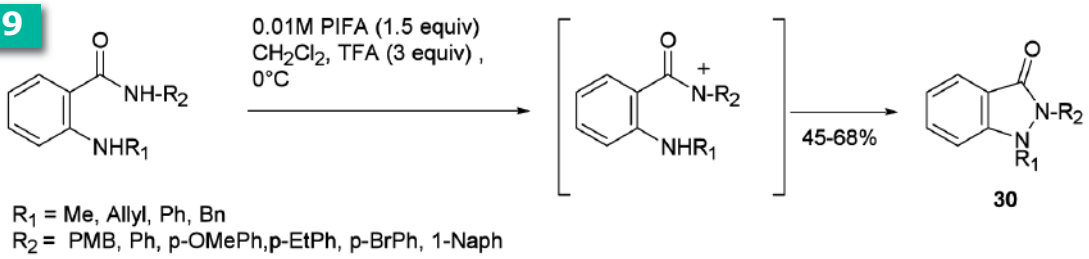
Scheme 18



[20] Huang, L-J.; Shih, M-L;; Chen, H-S.; Pan, S-L.; Teng, C-M.; Lee, F-Y.; Kuo, S-C. *Bioorg. Med. Chem.* **2006**, *14*, 528.
[21] Lee, J.; Choi, H.; Kim, K-H.; Jeong, S.; Park, J-W.; Baek, C-S.; Lee, S-H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2292.
[22] Counceller, C. M.; Eichman, C. C.; Wray, B. C.; Stambuli, J. P. *Org. Lett.* **2008**, *10*, 1021.

The synthesis of a series of 1*H*-indazol-3-ones with creation of the N-N bond has been achieved via the intramolecular trapping of an *N*-acylnitrenium intermediate by an *ortho*-disposed amino group[24]. Starting from an *o*-aminobenzamide the *N*-acylnitrenium cation was best generated by action of the hypervalent iodine reagent PIFA in DCM at 0°C (Scheme 19).

Scheme 19

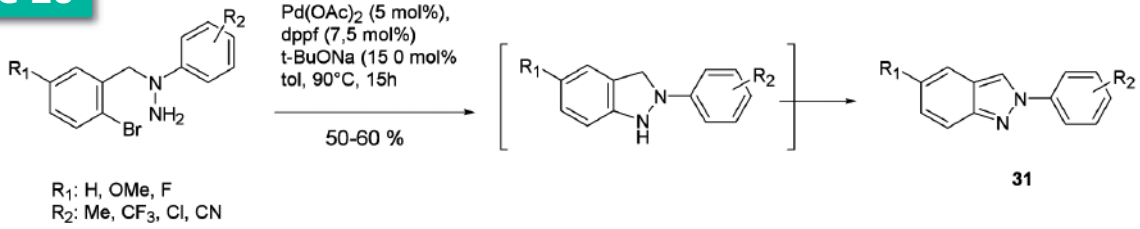


B. Methods for the preparation of *N*-2 substituted 2*H*-indazole compounds

1. Creation of a C-N bond

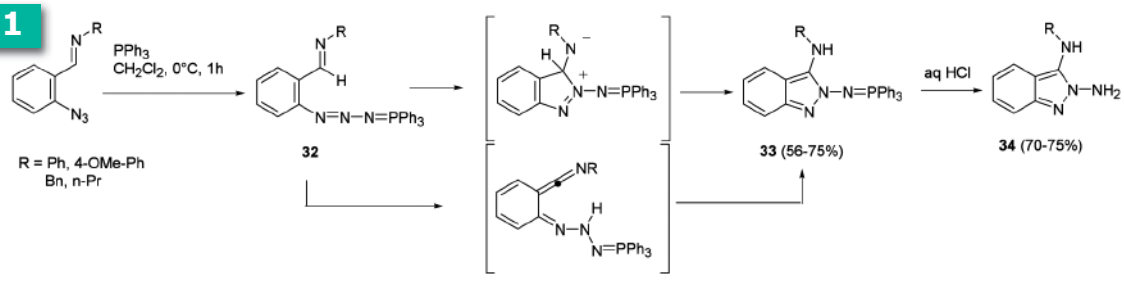
The chemistry of 2*H*-indazoles has not been explored as well as the chemistry of 1*H*-indazoles. However, the discovery that *N*-2 substituted 2*H*-indazole compounds may exhibit biological activities has generated recent interest in their simple and efficient preparation.
A synthesis of 2-aryl-2*H*-indazoles *via* a palladium-mediated intramolecular amination reaction of *N*-aryl-*N*-(*o*-bromobenzyl)-hydrazines has been reported by Song and Yee.[25] The best conditions to effect the transformation are heating in toluene at 90°C for 15h in the presence of $Pd(OAc)_2$ (5 mol%), dppf (7,5 mol%), and t-BuONa (15 0 mol%). Yields were comprised in the 50 to 60% range. The catalytic system is equally effective for electron-rich and electron-deficient substituents on both phenyl rings. In a mechanistic point of view the formation of the sp_2 C-N bond is followed by the spontaneous oxidation of the dihydroindazole intermediates to give the 2-aryl-2*H*-indazole products (Scheme 20).

Scheme 20



Molina et al.[26] reported the preparation of 2,3-diamino-2*H*-indazoles by treatment of *o*-azidobenzaldimines with tertiary phosphines followed by acidic hydrolysis. The reaction led first to the formation of 2*H*-indazole derivatives **33** whose subsequent hydrolysis furnished the 2,3-diamino-2*H*-indazoles **34**. The transformation may be accounted for by an initial Staudinger reaction to give a reactive phosphazide intermediate **32** followed by a cyclization reaction or by the formation of a ketenimine through a 1,5 sigmatropic shift and subsequent ring closure (Scheme 21).

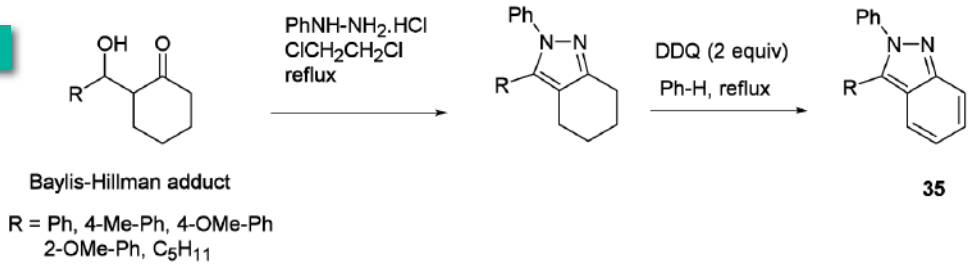
Scheme 21



[23] Matassa, V. G.; Maduskuie, Jr. T. P.; Shapiro, H. S.; Hesp, B.; Snyder, D. W.; Aharony, D.; Krell, R. D.; Keith, R. A. J. *Med. Chem.* **1990**, *33,* 1781.
[24] Correa, A.; Tellitu, I.; Dominguez, E.; SanMartin, R. J. *Org. Chem.* 2**006**, *71,* 3501.
[25] Song, J. J.; Yee, N. K. *Organic Lett.* **2000**, *2*, 519.
[26] Molina, P.; Arques, A.; Vinader, M. V. J. *Org. Chem.* **1990**, *55*, 4724.

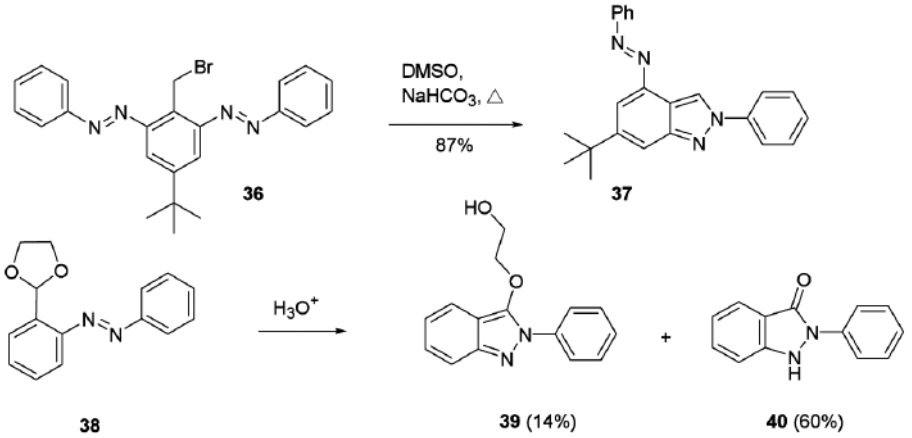
Starting from Baylis-Hillman adducts of cyclohexenone, a two-step procedure for the formation of *N*-Ph-2*H*-indazoles featuring DDQ oxidation of pyrazoles intermediates has been reported[27] (Scheme 22). Moderate overall yields were obtained (c.a 35%).

Scheme 22



German scientists[28] observed that several oxidation procedures, such as the Kornblum oxidation, applied to benzyl bromide **36**, instead of giving the expected aldehyde, led in fact to the 2-phenyl-2*H*-indazole compound **37**. In an other example, acidic hydrolysis of acetal **38** failed to give the corresponding aldehyde but led instead to a mixture of 2-phenyl-2*H*-indazole compound **39** and 2-phenyl-1*H*-indazol-3-one compound **40** (Scheme 23).

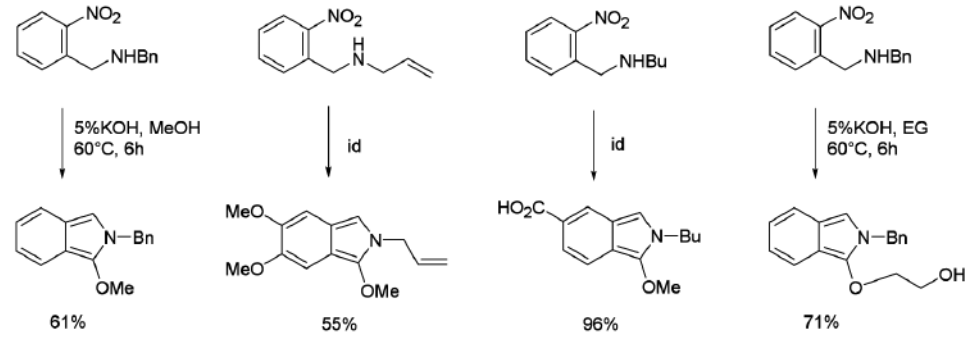
Scheme 23



2. Creation of the N_1-N_2 bond

A one-step synthesis of 3-alkoxy-2*H*-indazoles by heating *o*-nitrobenzylamines in a solution of 5% KOH in an alcoholic solvent has been reported by Kurth and coll.[29a] The starting amines were prepared from either *o*-nitrobenzylbromides or *o*-nitrobenzaldehydes in excellent yields. As shown in Scheme 24, an electron-withdrawing group in the starting o-nitrobenzylamine has a beneficial influence on the reaction productivity. Several other alcohols may be employed instead of methanol. A mechanism has been proposed to account for these transformations[29b]. This synthetic strategy was subsequently applied to generate a library of 2-alkyl-3-alkoxy-2*H*-indazole-6-carboxamides (200 compounds)[29c].

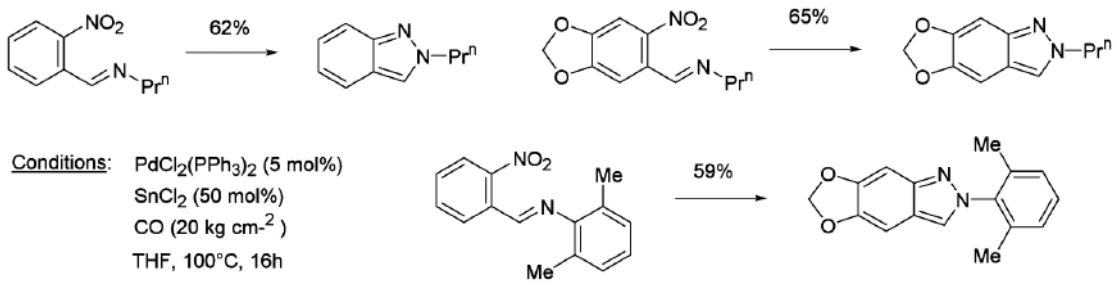
Scheme 24



[27] Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46,* 5387.
[28] Peters, M. V.; Stoll, R. S.; Goddard, R.; Buth, G.; Hecht, S. J. *Org. Chem.* **2006**, *71*, 7840
[29] a) Mills, A. D.; Nazer, M. Z.; Haddadin, M. J.; Kurth, M. J. J. *Org. Chem.* **2006**, *71,* 2687; b) Kurth, M. J.; Olmstead, M. M; Haddadin, M. J. J. *Org. Chem.* **2005**,*70*, 1060; c) Mills, A. D.; Maloney, P.; Hassanein, E.; Haddadin, M. J.; Kurth, M. J. J. *Comb. Chem.* **2007**, *9,* 171.

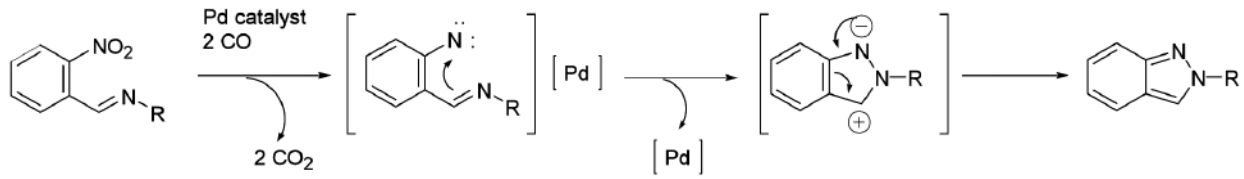
Akazome et al.[30] reported the palladium-catalyzed intramolecular reductive *N*-heterocyclization of (2-nitrobenzylidene)amines to give the corresponding 2*H*-indazole products in 48-75% isolated yields. Reactions were conducted in a stainless reactor at 100°C for 16h under 20 kg cm^{-2} of initial CO pressure and in the presence of a $PdCl_2(PPh_3)_2$ (5 mol%)-$SnCl_2$ (50 mol%) system. Some examples are shown in Scheme 25.

Scheme 25



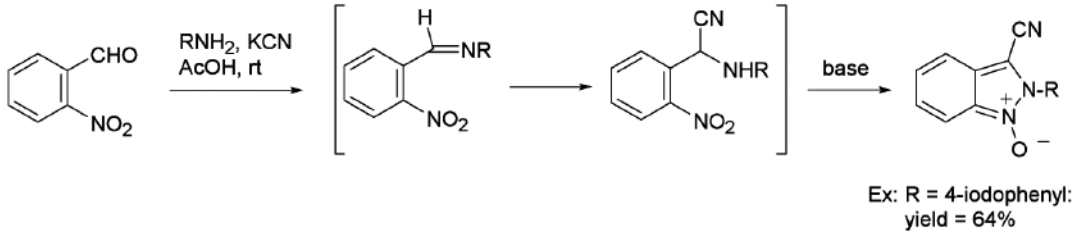
On the basis of experimental observations and deuterium labelling experiments, a mechanism involving the formation of a nitrene, intermediate, strongly coordinated to the metal, was postulated (Scheme 26).

Scheme 26



A series of 3-cyano-2*H*-indazole *N*[1]-oxides has been synthesized in order to evaluate the trypanocidal and leishmanocidal activities of each derivative[31]. Following the route shown in Scheme 27, *o*-nitrobenzaldehyde was first transformed, *via* a Schiff base, to an α-aminonitrile derivative which was next cyclized to a 3-cyano-2*H*-indazole *N*[1]-oxide by treatment with a base (Et_3N or $NaHCO_3$).

Scheme 27

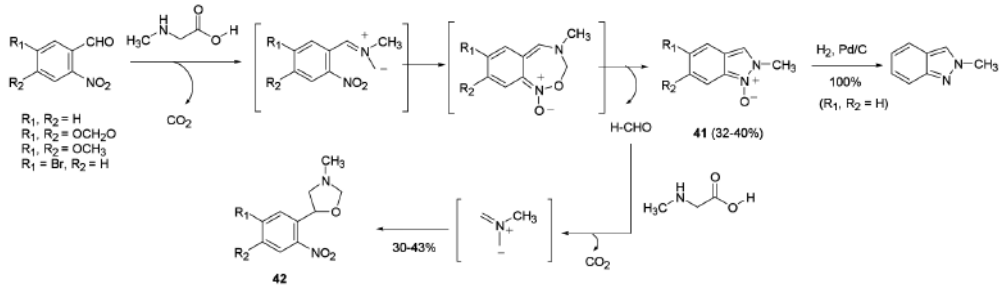


[30] Akazome, M.; Kondo, T.; Watanabe, Y. J. *Org. Chem.* **1994**, *59,* 3375

[31] a) Gerpe, A. ; Aguirre, G. ; Boaini, L. ; Cerecetto, H. ; Gonzáles, M. ; Olea-Azar, C.; Rigol, C.; Maya, J. D.; Morello, A.; Piro, O. E.; Arán, V. J.; Azqueta, A.; López de Ceráin, A.; Monge, A. ; Rojas, M. A. ; Yaluff, G. *Bioorg. Med. Chem.* **2006**, *14*, 3467. b) Gerpe, A. ; Piro, O. E. ; Cerecetto, H. ; González, M. *Journal of. Molecular Structure,* **2007**, *871*, 98.

Nyerges et al.[32] reported the synthesis of 2*H*-indazole-*N*[1]-oxides *via* a 1,7-electrocyclization reaction of azomethine ylides onto a nitro group. Thus, *o*-nitrobenzaldehyde reacted with sarcosine to generate, following a decarboxylative condensation process, an unstabilized azomethine ylide. The latter reacted with the nitro group to give, by way of a 1,7-electrocyclization, an oxadiazepine intermediate, which then undergoes a ring contraction to ultimately give the 2*H*-indazole-*N*[1]-oxides **41** in modest yield. The formaldehyde formed during the contraction step is trapped by the excess of sarcosine to give an azomethine ylide, which, by reaction with the starting *o*-nitrobenzaldehyde, led to an oxazolidine by-product **42**. Reduction of 2*H*-indazole-*N*[1]-oxide **41** (R_1,R_2 = H) led to the corresponding 2*H*-indazole (Scheme 28).

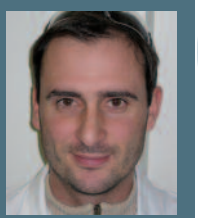
Scheme 28



[32] Nyerges, M. ; Virányi, A.; Zhang, W.; Groundwater, P. W.; Blaskó, G.; Tőke, L. *Tetrahedron,* **2004***, 60*, 9937; Nyerges, M. ; Fejes, I.; Virányi, A.; Groundwater, P. W.; Tőke, L. *Tetrahedron Lett.* **2001***, 42,* 5081.

Considerable efforts have been recently devoted to the development of new efficient methods for the preparation of 1*H*- and 2*H*-indazole compounds. These efforts may be accounted for by the fact that these compounds display a wide range of pharmacological activities and that common synthetic methods need relatively harsh conditions (strong acids and high temperatures). The reported recent developments should facilitate access to this important class of heterocycles and should increase interest for those involved in new drug discovery.

Presentation of a chemistry-biology team



Véronique Chesneau *est technicienne de laboratoire chez Atlantic Bone Screen depuis décembre 2005.* Titulaire d'un DUT Génie Biologique option Analyses Biologiques et Biochimiques et d'une spécialisation en recherche biomédicale, Véronique Chesneau a multiplié les expériences dans les laboratoires publics de recherche et dans les laboratoires de biotechnologie privés. Elle assure aujourd'hui une grande partie des essais *in vivo* chez ABS.

Le **Dr Mickaël Pauvert**, *Chef de projet chez AtlanChim Pharma depuis 5 ans, est titulaire d'un doctorat en chimie fine avec une spécialité en synthèse organique.* Après avoir réalisé un post-doctorat aux Etats-Unis, il a intégré la société AtlanChim à la création de celle-ci (novembre 2003). Il est en charge de l'organisation de la production au sein du Laboratoire, synthétise et optimise des contrats industriels de recherche en synthèse à façon de molécules complexes.

Veronique Chesneau is laboratory technician at Atlantic Bone Screen since December 2005. Having a "DUT Génie Biologique - option Analyses biologiques et biochimiques" (University diploma in biological engineering – Biological and biochemical analyses) and a specialization in biomedical research, Veronique Chesneau has had numerous professional experiences in public and private laboratories. Today she is in charge of a great part of in vivo assays at ABS.

Dr Mickaël Pauvert is head of project at AtlanChim Pharma since the creation of the company Atlanchim (2003). He has a doctorate in fine chemistry with a specialization in organic synthesis. He carried out a post-doctoral in the United States and joined Atlanchim. Dr Mickaël Pauvert is in charge of the organization of production inside the Laboratory, he synthesizes and optimizes research industrial contracts in custom-made synthesis of complex molecules.

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