Novel strategy for the preparation of 3-perfluoroalkylated-2*H*-indazole derivatives

Hassen Bel Abed, Nils Weißing, Jens Schoene, Jannik Paulus, Norbert Sewald, Marc Nazaré

PII: S0040-4039(18)30365-4
DOI: https://doi.org/10.1016/j.tetlet.2018.03.051
Reference: TETL 49820

To appear in: *Tetrahedron Letters*

Received Date: 21 January 2018
Revised Date: 15 March 2018
Accepted Date: 19 March 2018

Please cite this article as: Abed, H.B., Weißing, N., Schoene, J., Paulus, J., Sewald, N., Nazaré, M., Novel strategy for the preparation of 3-perfluoroalkylated-2*H*-indazole derivatives, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.03.051

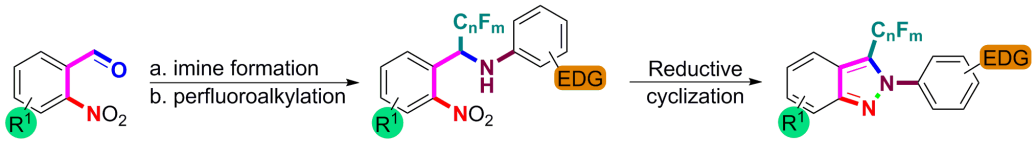
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Novel strategy for the preparation of 3-perfluoroalkylated-2*H*-indazole derivatives

Leave this area blank for abstract info.

Hassen Bel Abed, Nils Weißing, Jens Schoene, Jannik Paulus, Norbert Sewald and Marc Nazaré



R^1= H, Cl, F, CF_3, OCH_3, pyridine
EDG= OCH_3, SCH_3, CH_3
C_nF_m= CF_2H, CF_3, C_2F_5

10 examples
up to 97 % yield

Tetrahedron Letters
journal homepage: www.elsevier.com

Novel strategy for the preparation of 3-perfluoroalkylated-2*H*-indazole derivatives

Hassen Bel Abed,[a] Nils Weißing,[b] Jens Schoene,[a] Jannik Paulus,[b] Norbert Sewald[b] and Marc Nazaré[ac*]

[a]*Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), Campus Berlin-Buch, Robert-Roessle-Str. 10, 13125 Berlin, Germany*
[b]*Department of Chemistry, Bielefeld University, P.O. Box 10 01 31, 33501 Bielefeld, Germany*
[c]*Berlin Institute of Health (BIH), Anna-Louisa-Karsch-Str. 2, 10178 Berlin, Germany*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
2H-Indazole
Perfluoroalkylation
N-N bond formation
Ruppert-Prakash reagent
Reductive cyclization

ABSTRACT

A simple and novel methodology for the synthesis of 3-perfluoroalkylated-2*H*-indazole derivatives has been elaborated. The perfluoroalkylation of readily available 2-nitrobenzaldimines bearing electron donating groups was performed using the Ruppert-Prakash reagent and its analogues to afford α-difluoromethylated, α-trifluoromethylated and α-pentafluoroethylated benzylamines. A final reductive cyclization mediated by $SnCl_2$•$2H_2O$ led to 2*H*-indazoles containing perfluoroalkyl groups via the generation of a new N−N bond in moderate to good yields.

* Tel.: +49 3094063083; E-mail address: nazare@fmp-berlin.de

Fluorine substitution in bioactive molecules is considered essential in several research fields such as agrochemical, molecular imaging and medicinal chemistry. Around 20 % to 30 % of all newly approved drugs contain at least one fluorine.[1] The fluorine atom and its alkyl analogues have displayed unique properties to develop improved biologically active molecules with enhanced target affinity and metabolic stability.[2] The incorporation of perfluoroalkyl groups such as CF_2H, CF_3 and CF_2CF_3 into bioactive compounds has been extensively investigated[3] in the past decades and has resulted in the approval of diverse substances i.e. Celecoxib **1**, an anti-inflammatory drug containing a trifluoromethyl group[4] and Bixafen **2**, a cereal fungicide[5] bearing a difluoromethyl moiety. The pentafluoroethyl group has been introduced recently as a superior lipophilic analogue and its use in the synthesis of the selective estrogen receptor degrader (SERD) Fulvestrant **3** has prevented metabolic oxidation[6] (Figure 1). It is interesting to note the relevance of perfluoroalkylated pyrazole derivatives in the design of promising pharmacophores.

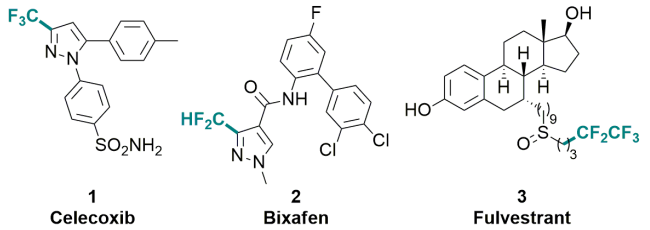
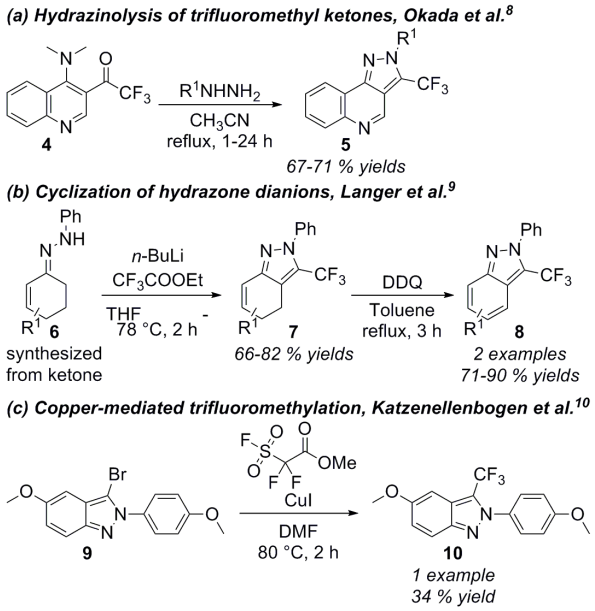


Figure 1. Perfluoroalkylated bioactive molecules.

Nevertheless, limited success has been reported towards the synthesis of perfluoroalkylated fused pyrazole analogues and especially for 2*H*-indazoles which have been recognized as novel privileged structures for the bioisosteric replacement of indoles and benzimidazoles.[7]



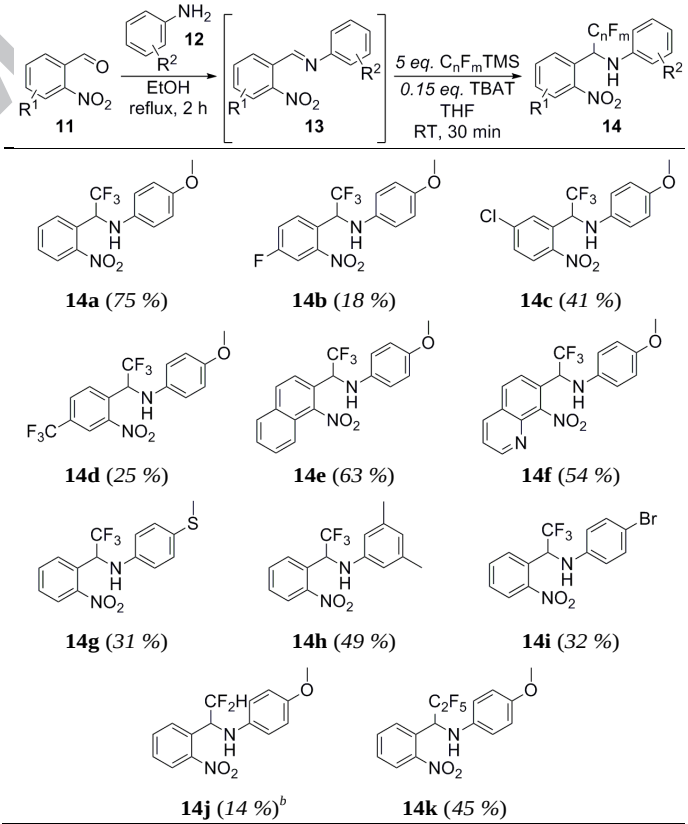
Scheme 1. Synthesis of perfluoroalkylated 2*H*-indazole analogues.

To the best of our knowledge, only the Okada group through the hydrazinolysis of trifluoromethyl ketones[8] **4** (Scheme 1a) and the Langer group via the cyclization of hydrazone dianions **6** with ethyl trifluoroacetate[9] (Scheme 1b) have addressed the synthetic accessibility to this scaffold. Additionally, Katzenellenbogen *et al.* have synthesized one single example of 3-trifluoromethyl-2*H*-indazole **10** using a copper-mediated coupling reaction with methyl 2,2-difluoro-2-(fluorosulfonyl)acetate as trifluoromethide precursor from 3-bromo-2*H*-indazole[10] **9** (Scheme 1c).

Considering the limited number of existing methods, the elaboration of a step-economical strategy starting from readily available substrates to access 2*H*-indazoles bearing perfluoroalkylated groups by an alternative approach is highly required. As part of our ongoing efforts in the synthesis of privileged structures[11] and 2*H*-indazole derivatives,[12] we report herein a simple and novel methodology for the preparation of 3-perfluoroalkylated-2*H*-indazoles from 2-nitrobenzaldehydes through a sequential imine formation/perfluoroalkylation/reductive cyclization.

The work started with the straightforward access to the 2-nitrobenzaldimines **13** by the reaction of 2-nitrobenzaldehydes **11** with aniline derivatives **12** in refluxing ethanol. **13** was then subjected to different described perfluoroalkylation conditions[13] which did not lead to the desired 2-nitro-α-perfluoroalkylated benzylamine substrates **14** or in traces amounts. The full conversion of the aldimine **13** into **14** was finally achieved by using the procedure developed by Prakash *et al.*[14] with 5 equivalents of perfluoroalkylating reagents instead of the initially described 1.5 equivalents which resulted in no or only partial conversion. A catalytic amount of tetrabutylammonium difluorotriphenylsilicate (TBAT)[15] was used to initiate the reaction performed in THF at room temperature.

Table 1. Synthesis of perfluoroalkylated benzylamine derivatives.[a]



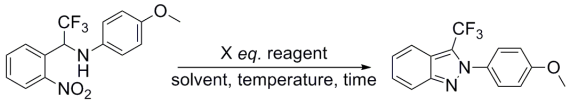
[a]Yields of isolated product over two steps and represent the average over at least two experiments. [b]Perfluoroalkylation was performed for 24 h.

These modified perfluoroalkylation conditions permitted the synthesis of nine α-trifluoromethylated benzylamines (**14a**-**14i**) with the Ruppert-Prakash reagent as well as one α-pentafluoroethylated derivative **14k** with C_2F_5TMS in moderate to good yields. It is noteworthy to mention that the possible introduction of a difluoromethyl group **14j** via the use of difluoromethyltrimethylsilane in extended reaction time i.e. 24

hours is due to the shorter length of the Si−CF_2H bond compared to Si−CF_3 bond.[16]

The second part of the investigation consisted in identifying suitable conditions for the formation of 2*H*-indazole **15a** through the deoxygenation of the nitroarene derivative **14a**. The use of organophosphorus reagents such as P(*n*-Bu)$_3$ did not lead to the desired heterocycle **15a** (Table 2, entry 1-2) while P(OEt)$_3$ afforded the 2*H*-indazole **15a** in only 16 % yield under neat conditions (Table 2, entry 3). The optimization was then directed towards Lewis acid-mediated reductive cyclization but $ZnCl_2$[17] did not improve the previous results (Table 2, entry 4). To our delight, $SnCl_2$•$2H_2O$[18] in ethanol at 75 °C resulted in 44 % yield (Table 2, entry 5) and the increase of equivalents of this reagent as well as a shorter reaction time allowed the synthesis of **15a** in 65 % yield (Table 2, entry 6). The replacement of ethanol by 2,2,2-trifluoroethanol (TFE) and ethylene glycol monomethylether (EGMM) did not provide better yields (Table 2, entry 7-8).

Table 2. Optimization of the reductive cyclization.[a]



14a **15a**

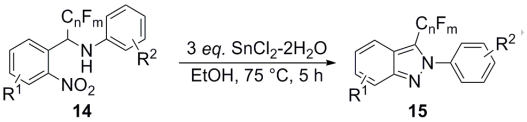
Entry	Reagent	X *eq.*	Time (h)	Solvent	Yield (%)[b]
1	P(*n*-Bu)$_3$	3	18	Toluene[c]	0
2	P(*n*-Bu)$_3$	3	18	DMF[c]	0
3	P(OEt)$_3$	3	18	–[c]	16
4	$ZnCl_2$	5	18	Toluene[c]	0
5	$SnCl_2$•$2H_2O$	1.5	18	Ethanol[d]	44
6	$SnCl_2$•$2H_2O$	3	5	Ethanol[d]	65
7	$SnCl_2$•$2H_2O$	3	5	TFE[d]	63
8	$SnCl_2$•$2H_2O$	3	5	EGMM[d]	52

[a]See supporting information for details. [b]Yield of isolated product. [c]Reaction was performed at 120 °C. [d]Reaction was performed at 75 °C.

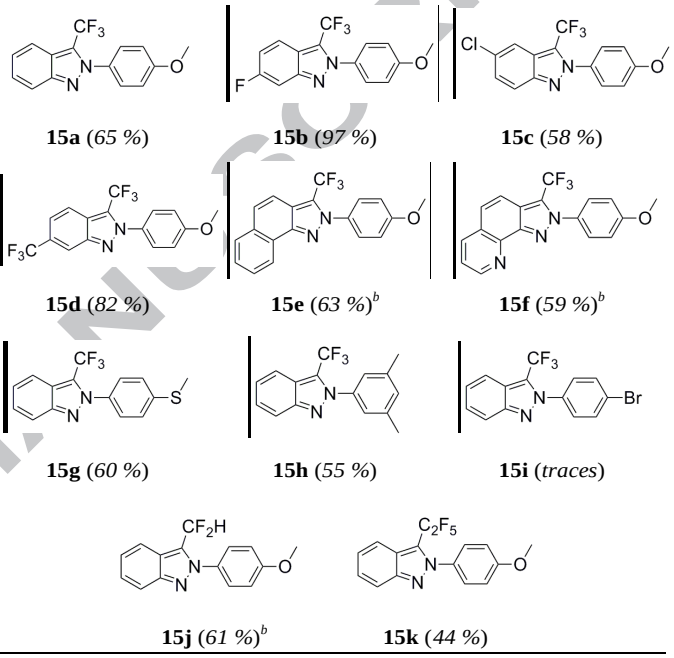
The synthesis of a small library of perfluoroalkylated 2*H*-indazole analogues was then initiated using the optimized reductive cyclization conditions. The investigation of the substrate scope focused at first on the nature of the 2-nitrobenzaldehydes and the incorporation of an additional fluorine delivered the trifluoromethylated heterocycle **15b** in excellent yield (97 %). The congener bearing a chlorine substituent **15c** was obtained in 58 % yield and could be used for further derivatization of the 2*H*-indazole. The attachment of a second trifluoromethyl group did not affect the deoxygenation and subsequent cyclization leading to **15d** in 82 % yield. Sterically hindered benzylamines were also tolerated such as **14e** and the quinoline substrate **14f** affording their corresponding 2*H*-indazole in good yields. We observed that variation on the aniline component was limited due to the reductive cyclization step, hence only anilines bearing electron-donating groups such as methoxy **15a**, thiomethyl **15g** and aliphatic group **15h** allowed the generation of the new N−N bond to form the expected heterocycle. The use of anilines possessing non-electron-donating groups did not give access to the 2*H*-indazole ring **15** but led to a full reduction of the nitro substituent to the corresponding acyclic amine. However, it was possible to observe traces of the brominated derivative **15i**. Finally, this approach facilitated the synthesis of hitherto unknown difluoromethylated **15j** and pentafluoroethylated **15k** structures.

The nucleophilicity of the α-perfluoroalkylated benzylamine **14** was critical to perform the reductive cyclization step. The presence of electron-donating groups attached to the aniline derivatives **12** was necessary to promote the formation of **15** and could be explained by the strong electron-withdrawing nature of the perfluoroalkyl groups at the α position lowering the nucleophilic behaviour of the benzylamine **14**.

Table 3. Synthesis of 3-perfluoroalkylated-2*H*-indazoles.[a]



14 **15**



15a (*65 %*) **15b** (*97 %*) **15c** (*58 %*)

15d (*82 %*) **15e** (*63 %*)[b] **15f** (*59 %*)[b]

15g (*60 %*) **15h** (*55 %*) **15i** (*traces*)

15j (*61 %*)[b] **15k** (*44 %*)

[a]See supporting information for details, yields of isolated product represent the average over at least two experiments. [b]Reaction was performed for 24 h.

In conclusion, we have elaborated a novel strategy to synthesize 3-perfluoroalkylated-2*H*-indazoles **15** through perfluorolkylation of readily available benzaldimines **13** followed by a reductive cyclization mediated by $SnCl_2$•$2H_2O$. The application of this methodology led to the synthesis of eight trifluoromethylated 2*H*-indazole analogues substituted by halides or sterically hindered groups on the 2-nitrobenzaldehyde **11** component. However, the reductive cyclization step required the use of anilines **12** bearing electron-donating groups in order to assist the generation of the new N−N bond. It is also the first report describing the preparation of the novel difluoromethylated 2*H*-indazole **15j** and pentafluoroethylated 2*H*-indazole **15k** derivatives. This approach represents a simple and novel alternative for the rapid access to 3-perfluoroalkylated-2*H*-indazoles and their evaluation as promising pharmacophores.

Acknowledgements

This Letter is dedicated to Mongi Bel Abed, an exceptional father (10/08/1951-16/01/2017). The authors thank Edgar Specker for recording the HRMS spectra, Peter Schmieder and Nils Trieloff for NMR assistance. We thank the Berlin Institute of Health (BIH) and the Helmholtz Drug Research for financial support.

References and notes

1. (a) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432-2506. (b) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422-518.
2. (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881-1886. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320-330. (c) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315-8359. (d) Huchet, Q. A.; Kuhn, B.; Wagner, B.; Kratochwil, N. A.; Fischer, H.; Kansy, M.; Zimmerli, D.; Carreira, E. M.; Müller, K. *J. Med. Chem.* **2015**, *58*, 9041-9060.
3. (a) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1-PR43. (b) Mykhailiuk, P. K. *Chem. Eur. J.* **2014**, *20*, 4942-4947. (c) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, *115*, 765-825. (d) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683-730. (e) Mykhailiuk, P. K. *Angew. Chem. Int. Ed.* **2015**, *54*, 6558-6561.
4. Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347-1365.
5. Dunkel, R.; Rieck, H.; Elbe, H.-L.; Wachendorff-Neumann, U.; Kuck, K.-H. WO 2003/070705.
6. Croxtall, J. D.; McKeage, K. *Drugs* **2011**, *71*, 363-380.
7. Cerecetto, H.; Gerpe, A.; González, M.; Arán, V. J.; de Ocáriz, C. O. *Mini-Rev. Med. Chem.* **2005**, *5*, 869-878.
8. (a) Okada, E.; Hatakenaka, M.; Sakaemura, T. *Heterocycles*, **2015**, *90*, 1072-1081. (b) Hatakenaka, M.; Adachi, S.; Okada, E. *Heterocycles*, **2016**, *92*, 936-943.
9. Ngo, T. N.; Ejas, S. A.; Hung, T. Q.; Dang, T. T.; Igbal, J.; Lecka, J.; Svigny, J.; Langer, P. *Org. Biomol. Chem.* **2015**, *13*, 8277-8290.
10. Angelis, M. D.; Stossi, F.; Carlson, K. A.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2005**, *48*, 1132-1144.
11. (a) Bel Abed, H.; Mammoliti, O.; Van Lommen, G.; Herdewijn, P. *Tetrahedron Lett.* **2012**, *53*, 6489-6491. (b) Bel Abed, H.; Mammoliti, O.; Van Lommen, G.; Herdewijn, P. *Tetrahedron Lett.* **2013**, *54*, 2612-2614. (c) Bel Abed, H.; Mammoliti, O.; Bande, O.; Van Lommen, G.; Herdewijn, P. *J. Org. Chem.* **2013**, *78*, 7845-7858. (d) Bel Abed, H.; Bande, O.; Mammoliti, O.; Van Lommen, G.; Herdewijn, P. *Tetrahedron Lett.* **2013**, *54*, 7056-7058. (e) Bel Abed, H.; Mammoliti, O.; Bande, O.; Van Lommen, G.; Herdewijn, P. *Org. Biomol. Chem.* **2014**, *12*, 7159-7166. (f) Bel Abed, H.; Van Brandt, S. F. A.; Vega, J. A.; Gijsen, H. J. M. *Tetrahedron Lett.* **2015**, *56*, 4028-4030.
12. (a) Halland, N.; Nazaré, M.; R'kyek, O.; Alonso, J.; Urmann, M.; Lindenschmidt, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 6879-6882. (b) Bel Abed, H.; Schoene, J.; Christmann, M.; Nazaré, M. *Org. Biomol. Chem.* **2016**, *14*, 8520-8528. (c) Schoene, J.; Bel Abed, H.; Christmann, M.; Nazaré, M. *Tetrahedron Lett.* **2017**, *58*, 1633-1635.
13. (a) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757-786. (b) Pooput, C.; Dolbier, W. R., Jr.; Medebielle, M. *J. Org. Chem.* **2006**, *71*, 3564-3568. (c) Dilman, A. D.; Levin, V. V. *Eur. J. Org. Chem.* **2011**, *2011*, 831-841. (d) Beier, P.; Zibinsky, M.; Prakash, G. K. S. *Nucleophilic Additions of Perfluoroalkyl Groups. Organic Reactions*. **2016**, 1-492.
14. Prakash, G. K. S.; Mogi, R.; Olah, G. A. *Org. Lett.* **2006**, *8*, 3589-3592.
15. Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1996**, *61*, 6901-6905.
16. Hagiwara, T.; Fuchikami, T. *Synlett* **1995**, 717-718.
17. Shirtcliff, L. D.; Rivers, J.; Haley, M. M. *J. Org. Chem.* **2006**, *71*, 6619-6622.
18. (a) Yoo, C. L.; Fettinger, J. C.; Kurth, M. J. *J. Org. Chem.* **2005**, *70*, 6941-6943. (b) Sawant, D.; Kumar, R.; Maulik, P. R.; Kundu, B. *Org. Lett.* **2006**, *8*, 1525-1528. (c) Shi, D.-Q.; Dou, G.-L.; Ni, S.-N.; Shi, J.-W.; Li, X.-Y.; Wang, X.-S.; Wu, H.; Ji, S.-J. *Synlett* **2007**, 2509-2512.

Supplementary Material

Supplementary data (experimental procedures and spectral data) associated with this article can be found, in the online version, at XXX.

Highlights

- A novel methodology for the synthesis of 3-perfluoroalkylated-2H-indazoles
- Sequential imine formation, perfluoroalkylation and $SnCl_2$ mediated cyclization
- Rapid generation of "drug-like" 3-perfluoroalkylated indazole libraries.