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Solid Phase Synthesis of Functionalized Indazoles using Triazenes – Scope and Limitations

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Indazoles are important heterocycles as they are a substantial part in many drugs. In this study we present a modular synthesis of highly substituted indazoles *via* a strategy on solid supports. The heterocyclic nitrogen atoms are originated from diazonium salts being cleaved from triazene containing resins. The scope and limitations of this process are explored considering especially the competitive occurrence of triazines and the cleavage of hydrolyzed and traceless side products.

Introduction

Benzoannelated nitrogen heterocycles are known as interesting scaffolds to find compounds which possess high biological activity and are considered as a source of many privileged compound classes in medicinal chemistry.[1-7] In particular, some indazole-containing compounds have a substantial impact when used as therapeutic agents (**Figure 1**). Well-known examples are Bendazac (**A**)[8] which is an anti-inflammatory agent used as an anti-cataract drug and Benzydamine (**B**),[9] a serotonin 5-HT_3 receptor antagonist used to treat and prevent nausea and vomiting induced by cancer chemotherapy. Apart from this, famous indazole derivatives include DNA-intercalating agents as the benzothiopyranoindazole CI-958,[10] activators of the nitric oxide receptor,[11] immunosuppressors as Bindarit (**C**),[12] calmodulin antagonists such as DY-9760 (**D**),[13] and indazoles with anticancer activity as Lonidamine (**E**) (**Figure 1**).[14]

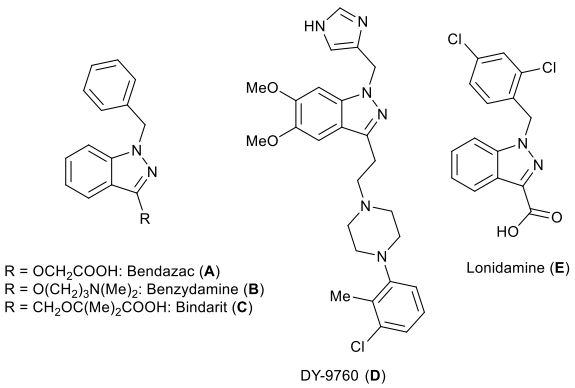


Figure 1 Molecules containing an indazole moiety with proven biological activity.

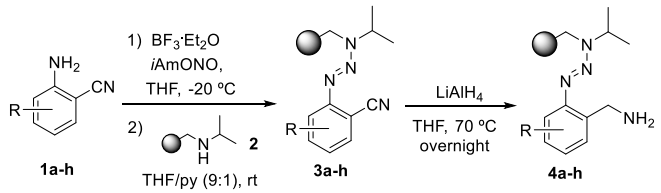
Moreover, indazoles are interesting molecules because they may act as bioisosters[15] of relevant heterocycles such as indoles[16] and benzimidazoles.[17] Unlike the latter ones, the indazole heterocycle is one of the at least exploited ones from the synthetic point of view, especially regarding to solid phase procedures.[18] While the solid phase organic synthesis (SPOS) of small-sized molecules has emerged as an important tool for the generation of heteroaromatic scaffolds in drug discovery,[19] there are only few reported examples for the synthesis of indazoles on solid phases.[20-22] Therefore, in order to benefit from the possibility of rapid syntheses without tedious and time-consuming purification steps, we intended to develop a straightforward method to gain diverse indazoles *via* solid phase chemistry. While according to the first synthesis of indazoles on solid supports,[20] the indazole unit was formed by a Lewis acid-catalyzed cyclization and the cleavage of the indazole from the solid phases in a second step, we decided to follow a route that will allow the formation of the indazole and cleavage off the resin in only one step.

We envisaged the triazene functionality to act as a suitable linker system to cleave indazoles as we observed the formation of a single 3-acylaminoindazole during the reaction of a 3,3-diisopropyltriazene derivative with an acyl chloride and subsequent acid-mediated cleavage of the triazene. This result has been gained in our group as a side-reaction in the solution phase synthesis of 3-acylbenzotriazines in 2009.[23] In the former procedure, the triazenes, which have been shown to be remarkably versatile starting materials for the liquid and solid phase synthesis of numerous nitrogen-based heterocycles,[6,24] had been used as a protected diazonium salt.[25,26]

Results and discussion

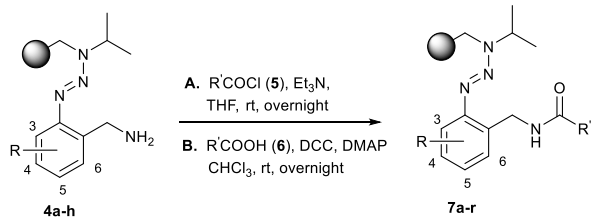
Encouraged by these results in conventional solution-phase reactions, we envisaged the development of an alternative route for the synthesis of indazole heterocycles on solid supports. This manuscript summarizes the novel established procedure for the solid phase synthesis and enlightens the influence of the substituents in the different positions of the molecule on the formation of the heterocyclic core. The immobilization of building

blocks on a polymeric support using the triazene T1 linker requires the syntheses of diazonium salts which were prepared by diazotization of *o*-aminobenzonitriles **1a-h** with isoamylnitrite. Their subsequent coupling with isopropylaminomethylpolystyrene **2** yielded triazene resins **3a-h** according to described procedures.[23] While almost all literature-known reactions on solid phases using the triazene linkers have been performed with a benzylaminomethylpolystyrene backbone,[6] we switched to the given isopropyl-derivative (**2**) in order to reflect the conditions of the successful reaction in solution as good as possible. Subsequently, the nitrile groups of the immobilized triazenes **3a-h** were reduced to the corresponding amines by using a solution of lithium aluminium hydride in tetrahydrofuran (**Scheme 1**).



Scheme 1 Synthesis of the triazene resins **4a-h**.

Table 1 Synthesis of acylated resins **7a-r**.

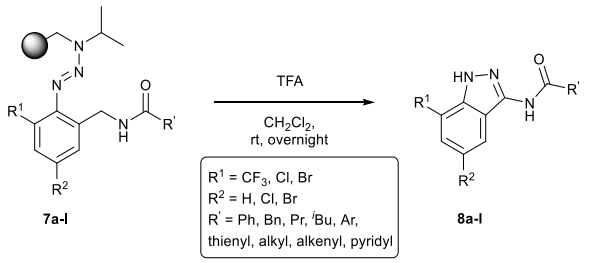


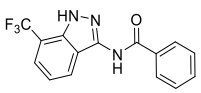
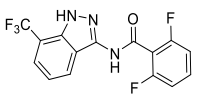
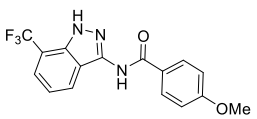
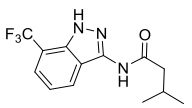
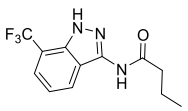
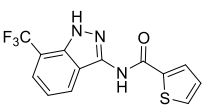
Resin 4	R	method	R'	Resin 7
4a	3-CF_3	A	phenyl	**7a**
4a	3-CF_3	A	2,6-$F_2C_6H_3$	**7b**
4a	3-CF_3	A	4-$MeOC_6H_4$	**7c**
4a	3-CF_3	A	isobutyl	**7d**
4a	3-CF_3	A	*n*-propyl	**7e**
4a	3-CF_3	A	2-thiophenyl	**7f**
4a	3-CF_3	A	isobutenyl	**7g**
4a	3-CF_3	A	benzyl	**7h**
4a	3-CF_3	B	4-pyridyl	**7i**
4b	3-Cl, 5-Cl	A	phenyl	**7j**
4c	3-Br, 5-Br	A	phenyl	**7k**
4d	3-Cl	A	phenyl	**7l**
4a	3-CF_3	A	methyl	**7m**
4e	H	A	phenyl	**7n**
4f	4-Cl	A	phenyl	**7o**
4g	5-F	A	phenyl	**7p**
4h	5-Cl	A	phenyl	**7q**
4a	3-CF_3	B	4-IC_6H_4	**7r**

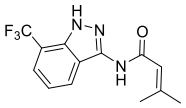
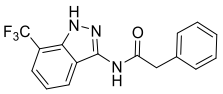
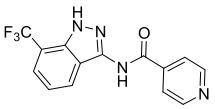
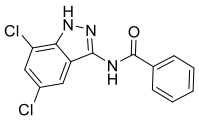
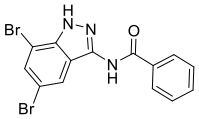
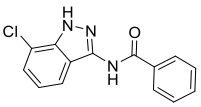
Resins **4** where then modified *via* the formation of an amide bond which has been carried out to give resins **7** (**Table 1**) *via* two different ways: (A) an acylation strategy of the amine **4** with the corresponding acyl chloride **5** in the presence of triethylamine or (B) the coupling between the amine **4** and the carboxylic acid **6** by using the coupling reagents DCC and DMAP. The latter procedure allows a wide variety of substituents on the introduced building block due to the large amount of carboxylic acids that are commercially available.

The cleavage of resins **7** was performed with trifluoroacetic acid in anhydrous dichloromethane in order to obtain the desired indazoles (**8**) (**Table 2**). According to the conventional synthesis in solution,[23] the resin **4a**, including 2-amine-3-trifluoromethylbenzonitrile as starting material, coupled with several acyl chlorides/carboxylic acids was chosen as starting material for the first experiments. Independent of the nature of the second building block (carrying R'), we could obtain the target indazoles (**8a-8i**) in moderated yields (29-34%) on solid phases if R' was not methyl. Several substituents in position R' have been introduced to the immobilized compounds **7** including aromatic, aliphatic, a thienyl, an alkenyl and a pyridyl residue without being able to find crucial differences concerning the success of the given synthetic route. Moreover, changing of the original 3-trifluoromethylbenzonitrile building block (**1a**) to 3-chlorine and 3-bromine-substituted benzonitriles (**1b-d**) we could obtain also the corresponding indazoles (**8j-8l**) in moderated yields.

Table 2 Cleavage of solid supported triazenes to give heterocycles **8a-l.**



Indazole	R^1/R^2	R'	structure	Yield [%]
8a	R^1 = CF_3, R^2 = H	phenyl		31
8b	R^1 = CF_3, R^2 = H	2,6-$F_2C_6H_3$		30
8c	R^1 = CF_3, R^2 = H	4-$MeOC_6H_4$		30
8d	R^1 = CF_3, R^2 = H	isobutyl		30
8e	R^1 = CF_3, R^2 = H	*n*-propyl		34
8f	R^1 = CF_3, R^2 = H	2-thiophenyl		30

8g	$R^1 = CF_3$, $R^2 = H$	isobutenyl		31
8h	$R^1 = CF_3$, $R^2 = H$	benzyl		34
8i	$R^1 = CF_3$, $R^2 = H$	4-pyridyl		29
8j	$R^1 = R^2 = Br$	Ph		29
8k	$R^1 = R^2 = Br$	Ph		26
8l	$R^1 = Cl$, $R^2 = H$	Ph		30

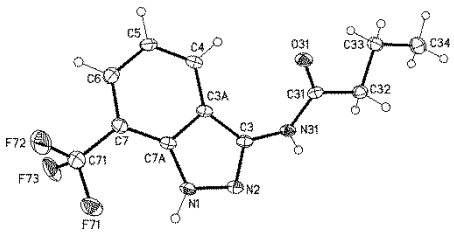
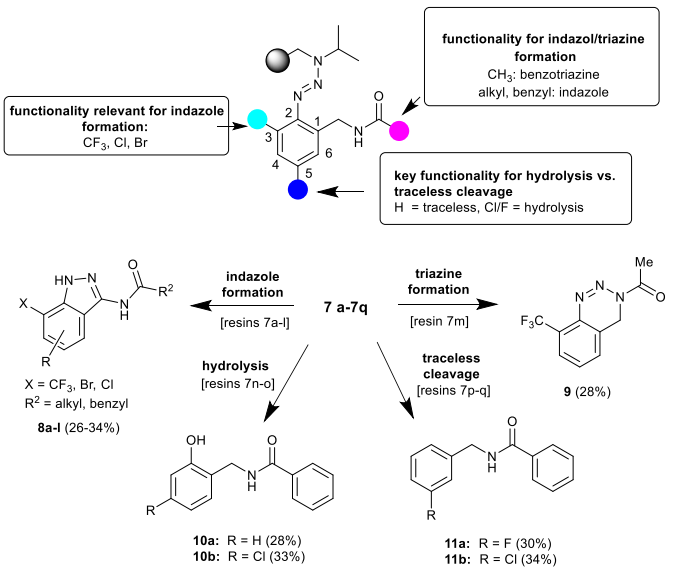


Figure 2 Molecular structure of **8e** in the crystal (minor part of the disordered F-atoms omitted for clarity, displacement parameters are drawn at 50% probability level).

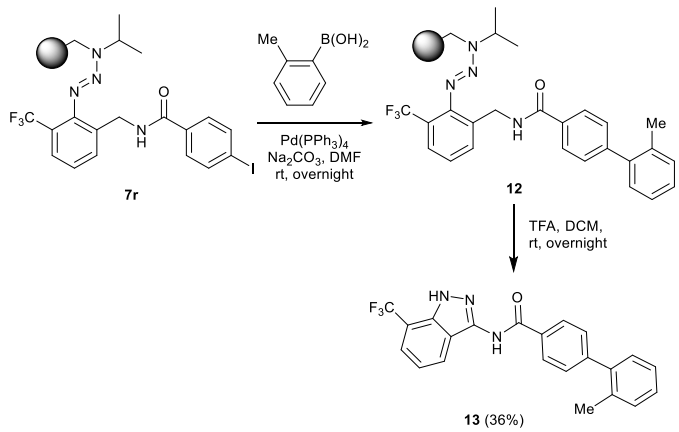
While the reactions of resins **7** including residues R' larger than methyl gave the desired indazoles, which could be confirmed by crystallizing the compound **8e** and investigation *via* X-ray crystallography (**Figure 2**), the reaction of resin **4a** with acetyl chloride followed by cleavage of the resulting resin **7m** gave not the expected indazole but the related benzotriazine **9** as it was isolated in solution phase approaches (**Scheme 2**). In accordance with the former results,[23] we assume that if 3-isopropyl-2-(trifluoromethyl)phenyl)triaz-1-enes are used as possible source of triazine vs. indazole formation, precursors bearing a methyl residue R' favor the formation of benzotriazines (**9**) while precursors bearing a residue R' larger than methyl favor the formation of indazoles (**8**).

Further experiments have been conducted to examine the scope of the indazole formation on solid supports. Besides the successfully used resins **4a-d**, carrying electron withdrawing substituents in ortho-position to the triazene linkage, other amine building blocks were selected (**1e-1h**) giving resins **4e-h** that have been used for the presented synthetic procedure. It has been shown that the substitution in ortho-position as given in resins **7a-l** is mandatory for the cleavage of indazoles from solid supports. Resins where the ortho-position remains unsubstituted (**7n-q**) do not yield indazoles *via* the herein presented procedure. The examination of the cleavage products of the latter resins showed that, depending on the substitution pattern of the triazene-containing aromatic moiety, either the hydrolysis or the traceless cleavage product has been formed (**10a-b** or **11a-b** respectively). We assume that giving an unsubstituted ortho-position, especially the para-position (to the triazene-linkage) has strong influence on the formation of the compounds of type **10** or **11** due to the possible diazonium salt stabilization.[27] If an atom with a lone pair electron is present in 5-position as e.g. a chlorine, it can stabilize the positive charge of the diazonium moiety, whereas if the chlorine atom is in 4-position, this conjugation is not possible and traces of water presented in trifluoroacetic acid could attack the salt to yield the hydrolyzed product (**Scheme 2**). It is important to remark that these four different products (traceless **11**, hydrolyzed **10**, indazole **8,** and the triazine derivative **9**) are obtained exclusively without traces of the others, that means the cyclization takes a different way depending on the substitution of the initial benzonitrile. In other words, the stability of the resulting diazonium salt after cleavage, that strongly depends on the nature of the ortho- and para-position, has a strong influence on the cyclization step.



Scheme 2 Products obtained *via* cleavage of resins 7**a-q** and dependencies regarding three points of diversity.

The herein presented procedure was evaluated towards its potential to synthesize complex indazole heterocycles on solid supports and the newly established method was used for the introduction of additional arene functionality by a cross-coupling reaction. The polymer-bound aryl iodide **7r** was coupled with 2-methylboronic acid *via* a Suzuki reaction to form the triazene resin **12** in the presence of $Pd(PPh_3)_4$ as a catalyst (**Scheme 3**). After the cleavage, the indazole **13** was isolated in moderated yield of 36% on solid phase.



Scheme 3 Cross-coupling reaction on solid supports and subsequent cleavage to give indazole **13**.

Conclusions

In this study, we present a modular synthesis of highly substituted indazoles on solid supports. The scope and limitations of this process are explored and side products are identified. The modularity has been demonstrated by a synthetic procedure consisting of five steps using three different building blocks of which one could be successfully introduced *via* an on-bead modification by Suzuki coupling. Only moderate yields have been shown for the cleaved target compounds but the purity of the crude material allowed fast purification *via* flash chromatography. The solid supported reaction furnished enough material for biological evaluations *via* a straightforward protocol using only commercially available compounds. The herein developed methodology enables the extension of the protocol to increase the diversity of the synthesized indazoles in future applications offering a novel access to libraries of nitrogen-rich heterocycles with fluorine substitution patterns

Acknowledgements

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Single crystal structure determination of 8e

The Single crystal X-ray diffraction study of **8e** was carried out on Bruker-Nonius KappaCCD diffractometer at 123 K using MoKα radiation (λ= 0.71073 Å). Direct methods (for **8e**, SHELXS-97)[28] were used for structure solution and refinement was carried out using SHELXL-2014[28] (full-matrix least-squares on F^2). Hydrogen atoms were localized by difference Fourier synthesis map and refined using a riding model [H (N) free]. A semi-empirical absorption correction was applied. The trifluoromethyl group is disordered.

Compound **8e**: $C_{12}H_{12}F_3N_3O$, Mr = 271.25 g mol^{-1}, colourless crystals, size 0.30 × 0.06 × 0.04 mm, triclinic P-1 (no.2), a = 4.8788(4) Å, b = 10.1605(6) Å, c = 12.1307(9) Å, α = 79.331(5)°, β = 81.744(7)°, γ = 86.251(5)°, V = 584.35(7) $Å^3$, Z = 2, D_{calcd} = 1.542 Mg m^{-3}, F(000) = 280, μ = 0.134 mm^{-1}, T = 123 K, 6971 measured reflections ($2\theta_{max}$= 55°), 2681 independent reflections [R_{int}= 0.032], 206 parameters, 83 restraints, R_1 [for 2010 I › 2σ (I)] = 0.042, wR_2 (for all data) = 0.104, S = 1.04, largest diff. peak and hole = 0.320 e $Å^{-3}$/-0.233 e $Å^{-3}$.

Supplementary data

Electronic Supplementary Information (ESI) available: crystallographic data in cif-format (**8e**) and synthetic procedures and characterization for synthesized compounds (**8a-8l**, **9**-**13**). See DOI: 10.1039/b000000x/. The primary data of the cleaved indazoles are available *via* the online repository chemotion (www.chemotion.net).

Crystallographic data (excluding structure factors) for the structure reported in this work have been deposited with Cambridge Crystallographic data Center as supplementary publication no. CCDC-1038684 (**8e**). Copies of the data can be obtained free of charge on application to the Direct, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223) 336033: e-mail: deposit@ccdc.cam.ac.uk.

Notes and references

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