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Synthesis of Substituted Indazole Acetic Acids by N–N Bond Forming Reactions

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Herein, we report on the discovery and development of novel cascade N–N bond forming reactions for the synthesis of rare indazole acetic acid scaffolds. This approach allows for convenient synthesis of three distinct indazole acetic acid derivatives (unsubstituted, hydroxy, and alkoxy) by heating 3-amino-3-(2-nitroaryl)propanoic acids with an appropriate nucleophile/solvent under basic conditions. The reaction tolerates a range of functional groups and electronic effects and, in total, 23 novel indazole acetic acids were synthesized and characterized. This work offers a valuable strategy for the synthesis of useful scaffolds for drug discovery programs.

Introduction

Indazole containing scaffolds (Figure 1) can be found in numerous biologically active compounds[1] including the approved nonsteroidal anti-inflammatory drugs bendazac[2] and benzydamine,[3] the 5-HT_3-receptor antagonist granisetron[4] (used to prevent nausea) and the anticancer agents axitinib,[5] niraparib[6] and pazopanib.[7] More generally, indazoles are routinely used by medicinal chemists in scaffold-hopping[8] and fragment-based drug design[9] campaigns due to their unique physicochemical properties, hydrogen bonding capabilities[10] and similarity to the privileged indole[11] and benzimidazole[12] motifs. Furthermore, indazoles have been employed as phenol bioisosteres to tune pharmacokinetic and pharmacodynamic properties in early drug discovery programs.[11a,13]

Given their widespread importance, significant effort has been put into developing synthetic methods to access the indazole core.[14] The vast majority of the current approaches hinge on incorporation of the N–N motif via a hydrazine precursor[15] or formation of a diazo species.[16] In contrast, strategies involving formation of an N–N bond[17] and, in particular, those that provide access to 1*H*-indazoles are relatively unexplored. Although they offer valuable entry points into this important class of compounds, these methods often require the use of expensive transition metal catalysts[1a,18] or the preparation of advanced reactive intermediates.[19] Accordingly, new methods that avoid these drawbacks are highly desirable.

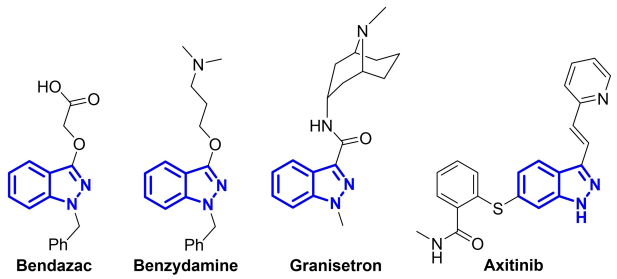

Figure 1. Drug molecules containing the 1*H*-indazole scaffold.

We previously reported a high-yielding synthesis of 1-*N*-hydroxyindazoles by base-mediated condensation of readily available 2-nitrobenzylamines.[20] In further extension of this work (Scheme 1) we were surprised to discover that while simple 2-nitrobenzylamine derivatives were smoothly transformed into 1-*N*-hydroxyindazoles, the related 3-aminopropanoic acid **1a** yielded an unexpected product. Subsequent analysis identified the product as the previously unreported 2-(1*H*-indazol-3-yl)-2-methoxyacetic acid **2a**, characterized by the unusual incorporation of an α-methoxy group, rather than the anticipated 1-hydroxyindazole species. Given the potential to access novel indazole derivatives from simple β-amino acid derivatives under transition metal-free conditions, we herein report our evaluation of the scope and limitations of this process.

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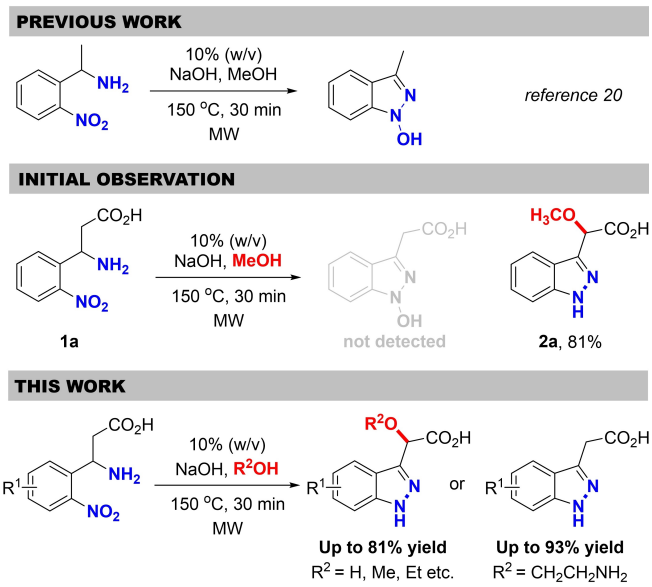


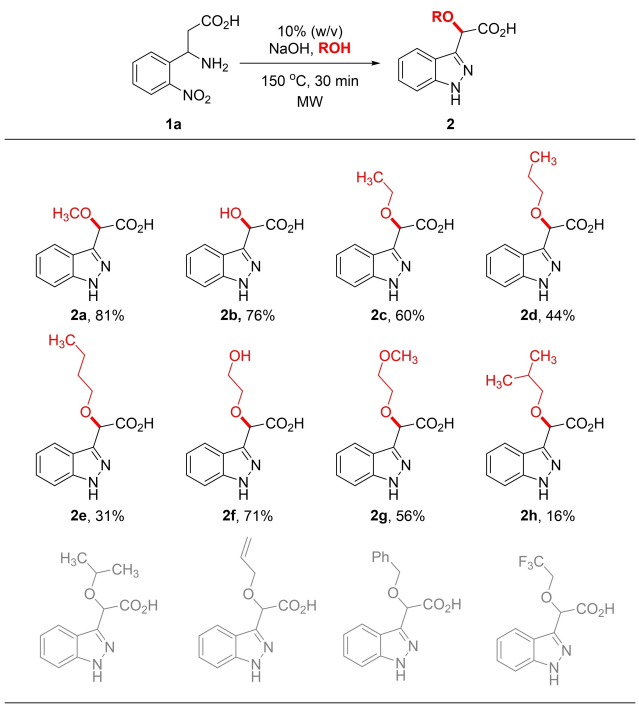
Scheme 1. Contrasting reactivities observed in base-catalysed cyclizations of 2-nitrobenzylamine derivatives.

Results and Discussion

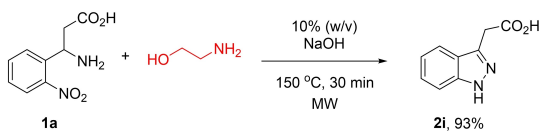
We initially evaluated a variety of alcohols as potential substrates for their reaction with 3-amino-3-(2-nitrophenyl)propanoic acid **1a** (Scheme 2). A preliminary screening of reaction conditions revealed that lower temperatures or concentrations of base led to either incomplete consumption of **1a** or poor conversion to the target products. Microwave irradiation of **1a** in selected alcohols at high temperature (150 °C) yielded a range of alkoxyindazole acetic acids (**2a** and **2c**–**h**). Importantly, the structure of **2c** was confirmed by X-ray crystallographic analysis, confirming incorporation of the ethoxy substituent between the carboxylic acid and the indazole ring (see supporting information). We found methanol and ethanol to be productive solvents, yielding the desired products in good to excellent yields (**2a** and **2c**). However, we observed a reduction in yield when moving to higher alcohols, with longer chain lengths leading to progressively lower yields (compare **2c**–**e**). Pleasingly, the use of water as an unhindered nucleophile led to formation of the corresponding alcohol **2b** in good yield. The branched isobutanol furnished the corresponding product **2h** albeit in low yield, while reaction with the secondary alcohol isopropanol was unsuccessful due to repeated over pressurization events[21] (presumably a result of solvent decomposition). Unfortunately, the reaction with allyl or benzyl alcohol only led to complex reaction mixtures and only traces of product were observed with trifluoroethanol. Finally, we were pleased to note that additional polar groups such as an alcohol or a methoxy group was well-tolerated, returning good yields of the desired alkoxy products **2f** and **2g**.

Interestingly, when ethanolamine was used as the solvent, indazole acetic acid (**2i**) was obtained in excellent yield instead of the expected alkoxyacetic acid (Scheme 3). Similarly, the use of *N,N*-dimethylethanolamine also led to formation of indazole acetic acid, although the yield was reduced to 44% due to competing formation of the corresponding alkoxy derivative (LCMS analysis). These results illustrate that the developed protocol enables the synthesis of three distinct indazole acetic acid variants (unsubstituted, hydroxy and alkoxy) by selection of an appropriate nucleophile/solvent. The ability to synthesize a variety of structurally similar molecules, from a common building block, is of considerable interest in early drug discovery as it allows for the rapid exploration of subtle structural differences.

Next, we examined the effects of aryl ring-substituents on the cyclization of 3-amino-3-(2-nitroaryl)propanoic acids using the high yielding alcohols methanol, ethanol and ethanolamine (Scheme 4). Introduction of a chlorine atom in the 4-position did not exhibit any discernible effect on the overall reaction outcome and high yields were obtained (**2j** and **2k**). However, introduction of an electron-donating methoxy or benzyloxy



Scheme 2. Microwave assisted synthesis of hydroxy- and alkoxyindazole acetic acids **2a**–**h** from 3-amino-3-(2-nitrophenyl)propanoic acid **1a** and various alcohols. Percentages refer to isolated yields. Synthesis of the compounds in gray was unsuccessful.



Scheme 3. Base-Mediated condensation of 3-amino-3-(2-nitrophenyl)propanoic acid **1a** with ethanolamine leads to formation of indazole acetic acid **2i**.

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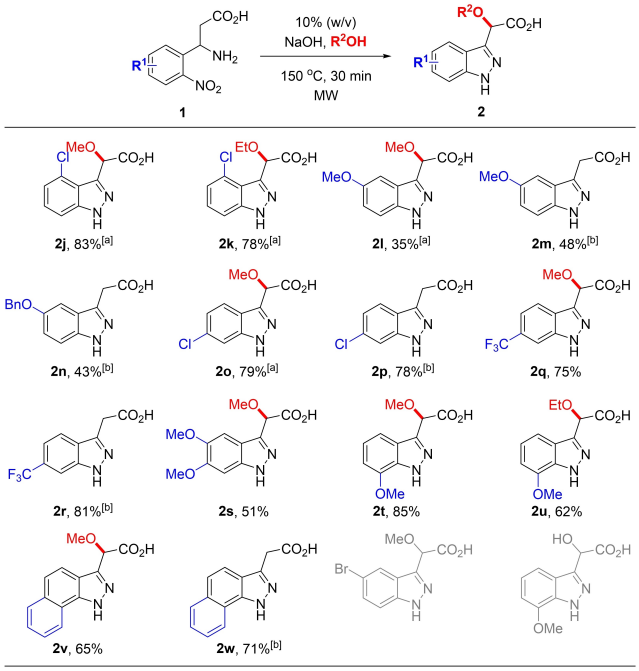
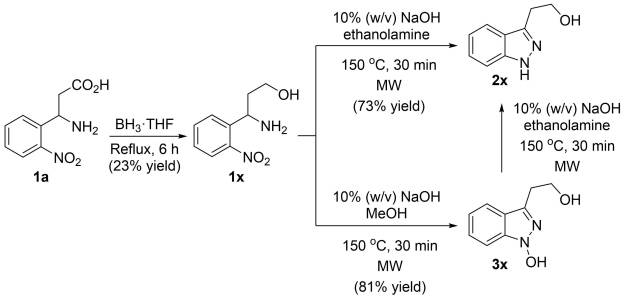


Scheme 4. Microwave assisted synthesis of indazole acetic acids **2j**–**w** from substituted 3-amino-3-(2-nitrophenyl)propanoic acids and various alcohols. Percentages refer to isolated yields. Synthesis of the compounds in gray was unsuccessful. [a] Reaction run at 170 °C. [b] Ethanolamine used as the solvent.

group in the 5-position led to a marked reduction in yield (**2l**–**n**). This may be attributed to the lowered electrophilicity of the putative nitroso intermediate **I**, see mechanism discussion below.[20] An electron-withdrawing 5-bromo substituent did not improve the outcome as it only led to formation of **2l** via competing nucleophilic substitution of the bromine by methoxide. The presence of electron-withdrawing chlorine (**2o** and **2p**) or trifluoromethyl (**2q** and **2r**) groups at the 6-position was well-tolerated furnishing good yields of the target compounds. The introduction of dimethoxy substitution at the 5- and 6-positions (**2s**) or a 7-methoxy substituent (**2t** and **2u**), gave the expected products in good to high yields (51-85%). Moreover, the benzo-fused analogs **2v** and **2w** were readily prepared by cyclization of the corresponding naphthyl starting material. Lastly, although full conversion was attained when water was utilized as the nucleophile with 3-amino-3-(3-methoxy-2-nitrophenyl)propanoic acid, the product was unstable and could not be isolated.

To explore the divergent reaction pathways observed upon cyclization of 2-nitrobenzylamines[20] or 3-amino-3-(2-nitroaryl)propanoic acids (leading to 1-hydroxyindazole or indazole acetic acids, respectively) **1a** was chemoselectively reduced with BH_3 to the primary alcohol **1x** and subjected to our reaction conditions (Scheme 5). Interestingly, treatment of **1x** with NaOH/MeOH led to exclusive formation of the 1-hydroxyindazole **3x**, whereas the reaction with NaOH/ethanolamine gave the 1*H*-indazole **2x** in 73% yield. The presence of a carboxylic acid proved crucial for alkoxylation, suggesting involvement of the acidic α-hydrogens and is consistent with

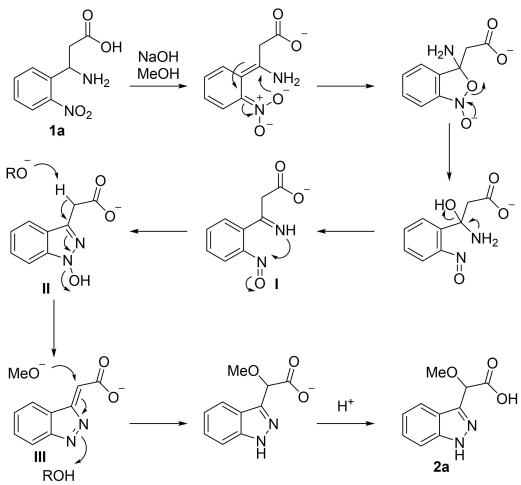


Scheme 5. Contrasting reactivities observed in the cyclizations of **1x** in the presence of NaOH and MeOH or ethanolamine.

our previous report.[20] In contrast, the ethanolamine mediated pathway is not dependent upon the presence of this moiety. This is in accordance with the known ability of ethanolamines to reduce nitrobenzene under basic conditions.[22] Notably, when the isolated 1-hydroxyindazole **3x** was treated with NaOH/ethanolamine direct deoxygenation to form **2x** was observed by LCMS analysis.

Based on these observations and literature precedent,[17c,23] a suggested mechanism is presented in Scheme 6. Initial oxygen transfer and elimination[23] leads to the nitroso intermediate **I** and subsequent intramolecular capture by the pendent imino group affords the indazole derivative **II**. Although isolation of **I** and **II** proved elusive, the formation of an intermediate with an *m/z* consistent with either of these structures was observed (LCMS analysis) when reactions were conducted at lower temperatures. Next, enolization and elimination of hydroxide gives the vinylogous imine derivative **III** followed by addition of the alkoxide nucleophile and acidic workup to deliver the indazole methoxyacetic acid product **2a**.

In the absence of a carbonyl group (as in **1x**) the intermediate corresponding to **II** cannot be deprotonated at the α-position and the hydroxyindazole **3x** is obtained as the



Scheme 6. Mechanistic rationale for the formation of **2a** from **1a** and MeOH/NaOH.

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main reaction product. When ethanolamine is used in this setting, it is likely that intermediate **II** is rapidly deoxygenated precluding formation of a Michael acceptor species (**III**) and subsequent incorporation of the alkoxy group into the side-chain.[24] Further work to delineate this deoxygenation process is currently ongoing in our laboratory.

Conclusions

In summary, our investigation has led to the discovery of two distinct heterocyclization reactions where 3-amino-3-(2-nitroaryl)propanoic acids can be transformed into 1*H*-indazoles in the presence of NaOH and various alcohols. When using simple alcohol solvents 2-alkoxyacetic acid derivatives were obtained in modest to excellent yields in a reaction that involves the formation of N–N and C–O bonds. In contrast, the reaction of 3-amino-3-(2-nitroaryl)propanoic acids with ethanolamine and sodium hydroxide resulted in exclusive formation of 2-indazole acetic acids without incorporation of the corresponding alkoxy group. Seemingly minor changes in conditions can have significant impact on the outcome of a reaction, and this work highlights the importance of exploring unexpected experimental observations. We hope that these methods will find utility in the synthesis of novel indazole scaffolds and applications in, for example, drug discovery programs.

Experimental Section

General methods: All reagents and solvents were of commercial quality and used without further purification. All reported yields are for isolated, homogenous and spectroscopically pure material. Silica gel chromatography was carried out on silica gel (60 Å pore size, particle size 40–63 nm) packed in glass columns. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz. The chemical shifts for ^{1}H NMR and ^{13}C NMR were referenced to tetramethylsilane via residual solvent signals (^{1}H: methanol-d_4 at 3.31 ppm, $CDCl_3$ at 7.26 ppm and DMSO-d_6 at 2.50 ppm; ^{13}C: methanol-d_4 at 49.0 ppm, $CDCl_3$ at 77.16 ppm and DMSO-d_6 at 39.52 ppm). LC/MS was performed on an instrument equipped with a CP-Sil 8 CB capillary column (50×3.0 mm, particle size 2.6 μm, pore size 100 Å) running at an ionization potential of 70 eV with a CH_3CN/H_2O gradient (0.05% HCOOH). Accurate mass values were determined via electrospray ionization with a 7-T hybrid ion trap and a TOF detector running in positive or negative mode. The microwave reactions were performed in a Biotage Initiator and the reaction temperature was determined using the built-in on-line IR-sensor. All reactions were performed in sealed microwave-transparent process vials designed for 2–5 mL reaction volumes. Melting point determinations were conducted on an Electrochemical Melting Point Apparatus and are uncorrected. Collection of X-ray data for compound **2c** was performed at the Latvian Institute of Organic Synthesis (Riga, Latvia).[25]

General procedure for the synthesis of compounds 2a–x and 3x

3-Amino-3-(2-nitrophenyl)propionic acid (Alfa Chemicals, 97%) (50 mg, 0.23 mmol) was added to a microwave vial (2–5 mL). A 10% w/v NaOH solution/suspension in the appropriate alcohol (2.5 mL) was prepared by adding the finely granulated NaOH and vortexing or sonicating thoroughly. The NaOH solution was added to the microwave vial and was sealed under air with a Teflon coated septum. After microwave irradiation for 30 min at 150 °C, using a fixed hold time, the solution was cooled and ethyl acetate (20 mL) and 1 M HCl (10 mL) were added. The organic phase was separated and the aqueous phase extracted twice more with ethyl acetate (10 mL). The combined organic phases were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. Purification was performed by silica gel flash chromatography with EtOAc/MeOH/HCOOH (100/0.5/0.5) as the eluent to afford the desired compounds.

Supporting Information

Additional references cited within the Supporting Information.[26]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: annulation · cyclization · Michael addition · nitrogen heterocycles · synthetic methods

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