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# Regioselective Synthesis of 2*H*-Indazoles Using a Mild, One-Pot Condensation–Cadogan Reductive Cyclization

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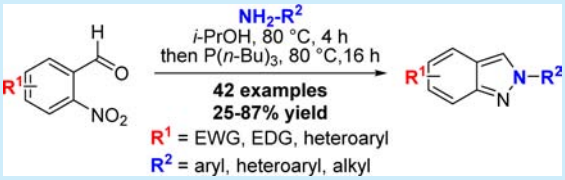
Supporting Information

**ABSTRACT:** An operationally simple and efficient one-pot synthesis of 2*H*-indazoles from commercially available reagents is reported. *Ortho*-imino-nitrobenzene substrates, generated via condensation, undergo reductive cyclization promoted by tri-*n*-butylphosophine to afford substituted 2*H*-indazoles under mild reaction conditions. A variety of electronically diverse *ortho*-nitrobenzaldehydes and anilines were examined. To further extend the scope of the transformation, aliphatic amines were also employed to form *N*2-alkyl indazoles selectively under the optimized reaction conditions.




The utility of 2*H*-indazoles as pharmacophores in drug discovery has been exemplified in several recent publications (Figure 1).[1] A substantial body of research exists around enabling the synthesis of such motifs.[2] Direct alkylation or arylation of 1*H*-indazoles frequently leads to mixtures of 1- and 2-substituted products in all but very specific cases.[3] As an alternative to direct substitution, considerable effort has been focused on cyclization reactions to selectively generate 2*H*-indazoles. The Cadogan indazole synthesis, or reductive cyclization of *ortho*-imino-nitrobenzenes mediated by triethyl phosphite, was one of the first methods described and remains one of the more effective synthetic transformations reported for this purpose.[4] Unfortunately, it carries the liabilities of being run in an excess of neat phosphite at relatively high temperatures on potentially high energy nitro/nitroso intermediates. Many variations on the reductive cyclization theme have been examined to address these concerns, including modifications to the original Cadogan conditions,[5] transition metal catalyzed reductive cyclizations of iminonitroaromatics,[6] and thermal/transition metal cyclization of 2-azidoimines.[7] A variety of other methods including reductive cyclizations of *ortho*-nitrobenyzlamines,[8] sydnone/benzyne cycloaddition,[9] zincate addition to diazonium salts,[10] intramolecular aminations,[11] and acylated azobenzene cyclizations have also been explored.[12] Many of these methods still carry limitations in terms of scope, use of transition metal catalysts, potential high energy intermediates at elevated temperature, and/or protracted syntheses of substrates. Consequently, there is still a need to develop an operationally simple and mild method to access this privileged pharmacophore starting from a broad class of readily available monomers.

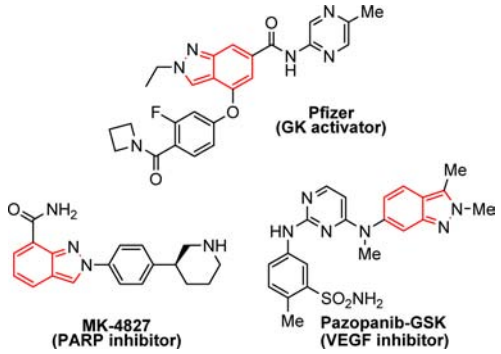



**Figure 1.** Indazole containing chemotherapeutics.

Of all the reported methods, we felt further optimization of the Cadogan conditions presented the best opportunity to develop a more general approach toward the synthesis of 2*H*-indazoles. Our efforts were focused on the identification of milder reaction conditions including lower temperatures and near stoichimetric amounts of reducing agent in a conventional solvent, ideally in tandem with, or subsequent to, imine formation in the same pot. While one-pot methods in various solvents have been reported, the reactions are frequently conducted at elevated temperatures (>150 °C) with microwave heating while maintaining the use of triethylphoshite as the reductant.

Under the generally accepted reaction mechanism (Figure 2), the phosphorus species reduces the nitro group sequentially

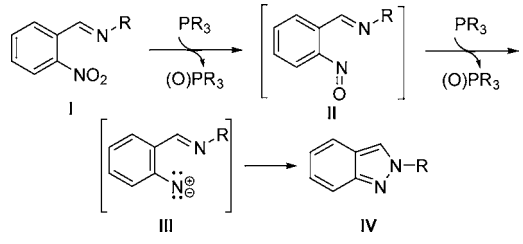



**Figure 2.** Proposed reaction mechanism.

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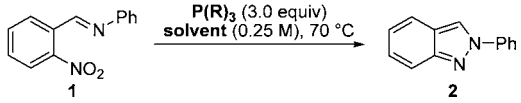
through addition across the NO bond in both starting material **I** and the presumed nitroso intermediate **II** to ultimately generate a nitrene or nitrene-like intermediate **III** which undergoes cyclization. The analogous nitroso compounds undergo reductive cyclization at or below room temperature, supporting the assumption that initial addition to the less reactive nitro species is typically the rate-limiting step. In examining the reaction mechanism and kinetics, Cadogan and co-workers profiled alternative phosphorus(III) reagents and demonstrated that the rate increased with increasing nucleophilicity of phosphorus.[13] While other reagents provided significant rate enhancement, triethyl phospite was adopted as the preferred reductant based on cost and availability. Trialkylphosphines were notably absent from these and subsequent studies. We reasoned that the initial reduction to nitroso intermediate **II** would occur appreciably faster with the more nucleophilic phosphine and provide conditions that might satisfy our requirements.

Our initial investigations commenced with the comparative evaluation of phosphites and phosphines to promote the reductive cyclization of *ortho*-imino-nitrobenzene **1** to indazole **2** (Table 1). We elected to use THF as a representative solvent

**Table 1. Optimization of Reductive Cyclization**[a]




1 2

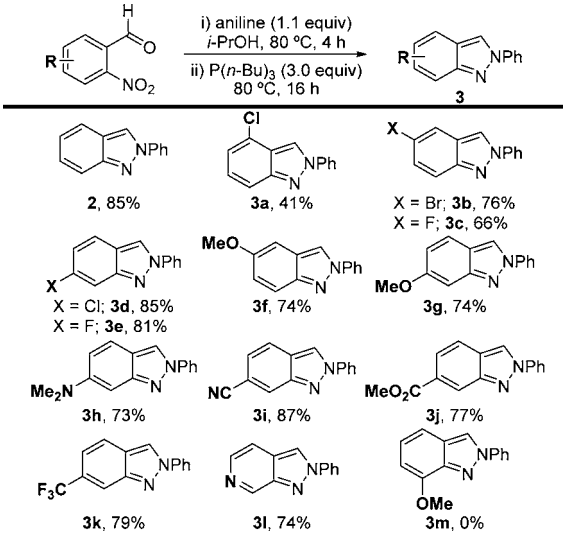
| entry | solvent | $P(R)_3$ | time (h) | yield (%)[b] |
|---|---|---|---|---|
| 1 | THF | $P(OEt)_3$ | 24 | 0 |
| 2 | THF | $P(Ph)_3$ | 24 | 0 |
| 3 | THF | $P(t\text{-}Bu)_3$ | 24 | 62[c] |
| 4 | THF | $P(Cyx)_3$ | 24 | 51[d] |
| 5 | THF | $P(n\text{-}Bu)_3$ | 24 | 74 |
| 6 | PhMe | $P(n\text{-}Bu)_3$ | 30 | 73 |
| 7 | EtOAc | $P(n\text{-}Bu)_3$ | 30 | 72 |
| 8 | MeCN | $P(n\text{-}Bu)_3$ | 24 | 73 |
| 9 | acetone | $P(n\text{-}Bu)_3$ | 24 | 62 |
| 10 | NMP | $P(n\text{-}Bu)_3$ | 24 | 63 |
| 11 | MeOH | $P(n\text{-}Bu)_3$ | 6 | 82 |
| 12 | EtOH | $P(n\text{-}Bu)_3$ | 6 | 77 |
| 13 | *i*-PrOH | $P(n\text{-}Bu)_3$ | 6 | 87 |

[a]See Supporting Information for optimization procedure. [b]Isolated yield after column chromatography. [c]Contained 61 wt % of imine **1**. [d]Contained 48 wt % of phosphine oxide.

and 3 equiv of phosphorus(III) reagent. While in theory 2 equiv of reagent should be sufficient for complete conversion, we chose to use an excess to protect against potential air oxidation, as all reactions were conducted with no special precautions with regards to anhydrous solvents or an inert atmosphere. It was immediately apparent triethyl phosphite and triphenylphosphine were not suitable reagents for the transformation, as no conversion was observed under the milder reaction conditions. Fortunately, more nucleophilic trialkylphosphines did demonstrate conversion to the desired product. Under the initial reaction conditions, tri-*tert*-butylphosphine afforded indazole **2** as well as unreacted starting material (Table 1, entry 3). Tricyclohexylphosphine provided complete conversion (Table 1, entry 4), however, removal of the phosphine oxide byproducts proved problematic and a less than ideal isolated yield resulted. Ultimately, tri-*n*-butylphosphine (Table 1, entry 5) provided complete conversion to indazole **2** in good yield with no complicating isolation issues. We next turned our attention to the effect of solvent on the reductive cyclization. Every solvent surveyed afforded the desired indazole in good yield (Table 1, entries 6–13). Significant rate enhancement and improved yields were observed when alcoholic solvents were employed. Conducting the reaction in *i*-PrOH provided the ideal conditions with desired product indazole **2** obtained in 87% isolated yield.

With the reductive cyclization conditions optimized, we turned our efforts toward developing a one-pot method to generate 2*H*-indazoles. As condensation of arylaldehydes and anilines occurs readily in *i*-PrOH at elevated temperature, it was envisioned that simply adding tri-*n*-butylphosphine after the condensation was complete, followed by heating, would afford the desired product without the complicating factor of isolating an imine intermediate. Fortunately, this method proved effective as the one-pot process afforded indazole **2** in 85% yield (Scheme 1).

**Scheme 1. Scope of Benzaldehyde Substitution**[a]




[a]The condensation of an *o*-nitrobenzaldehyde (1.0 equiv) with aniline (1.1 equiv) was carried out in *i*-PrOH (0.4 M) at 80 °C for 4 h in a 2-dram sealed vial, followed by cooling, treatment with $P(n\text{-}Bu)_3$ (3.0 equiv), and subsequent heating at 80 °C for a further 16 h.

After establishing optimized one-pot condensation–reductive cyclization conditions, the scope of the benzaldehyde was examined using commercially available *ortho*-nitroaldehydes (Scheme 1). Halogen containing aldehydes (**3a–e**) as well as electron-rich (**3f–h**), electron-deficient (**3i–k**), and heteroaromatic nitroaldehydes (**3l**) all provided desired products in moderate to good yield. The moderate yield observed for **3a** and no desired product observed in the attempted generation of **3m** suggests steric interactions or electron repulsion (either during the condensation or in the reductive cyclization, respectively) are a limitation to the scope of the method with respect to the aldehyde.

Similarly, we examined the scope of aniline and aminopyridine partners under our conditions (Scheme 2). Once again, halogen containing (**5a,d,g,m**), electron-rich (**5c,f,i**), and electron-deficient anilines (**5b,e,h,n**) all provided the desired products. Aminopyridines (**5j–l**) and sterically hindered anilines (**5o,p**) also undergo conversion to the indazole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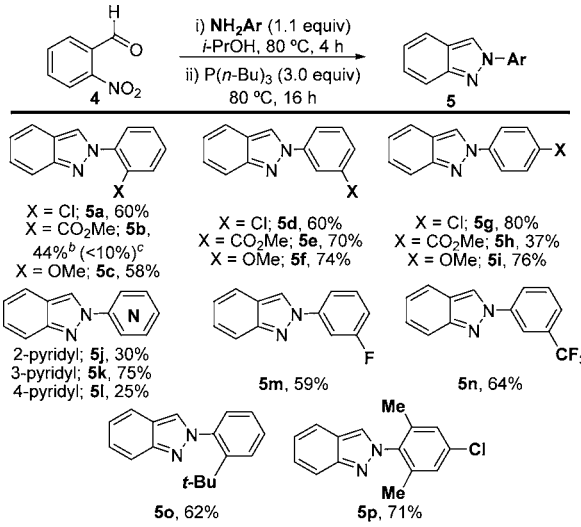
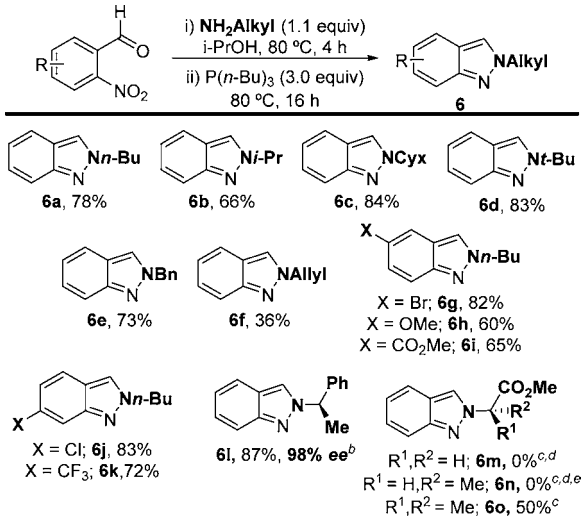
**Scheme 2. Scope of Aromatic Amines**[a]




[a]The condensation of *o*-nitrobenzaldehyde (1.0 equiv) with an aromatic amine (1.1 equiv) was carried out in *i*-PrOH (0.4 M) at 80 °C for 4 h in a 2-dram sealed vial, followed by cooling, treatment with P(*n*-Bu)$_3$ (3.0 equiv), and subsequent heating at 80 °C for a further 16 h. [b] Imine was preformed in toluene at reflux. [c] Isolated yield observed using a one-pot procedure.

**Scheme 3. Scope of Aliphatic Amines**[a]




[a]The condensation of *o*-nitrobenzaldehyde (1.0 equiv) with an aliphatic amine (1.1 equiv) was carried out in *i*-PrOH (0.4 M) at 80 °C for 4 h in a 2-dram sealed vial, followed by cooling, treatment with P(*n*-Bu)$_3$ (3.0 equiv), and subsequent heating at 80 °C for a further 16 h. [b] Determined by SFC using a chiral column. [c] Free base of the HCl salt was used. [d] Condensation conducted at rt over 12 h. [e] Reductive cyclization conducted at 50 °C.

products under the one-pot reductive cyclization conditions. Variability observed in the isolated yield when electron-deficient anilines were employed can be attributed to the relative stability of the imine intermediate. As illustrated in the case of **5b**, when the condensation was conducted under more forcing conditions an appreciable decrease in isolated yield was still observed. The electron-deficient imine intermediate appeared to be unstable under the reaction conditions, most likely due to an unfavorable equilibrium throughout the course of condensation leading to unproductive side reactions during the reductive cyclization.

While not well exemplified in the literature, Cadogan cyclization of aliphatic *ortho*-imino-nitrobenzenes is known.[13] In order to further demonstrate the scope of our method, we evaluated a variety of aliphatic amines under the standard conditions developed (Scheme 3). Straight chain (**6a**) as well as branched and cyclic primary amines (**6b–d**) were compatible with the optimized reaction conditions, providing the alkylindazole products in good yield. Fortunately, steric effects do not appear to impede the reductive cyclization pathway, as *tert*-butylamine was competent in providing indazole **6d**. Benzylamine worked well in generating indazole **6e**; however, allylamine provided indazole product **6f** in only moderate yield. The decreased reaction efficiency is presumably due to unproductive reaction pathways of the putative nitrene intermediate with the pendant olefin, which led to a complex mixture of undesired products.

As expected, altering the *ortho*-nitrobenzaldeyde coupling partner with aliphatic amines provided the desired indazole products (**6g–k**). Similar to the studies completed using aniline (Scheme 1), the electronic nature of the nitroaldehyde had little effect on the cyclization as electron-rich, electron-deficient, and halogen containing *ortho*-nitrobenzaldeydes were all compatible coupling partners with *n*-butylamine. Interestingly, using optically pure $\alpha$-methyl benzylamine in the reductive cyclization cascade provided the desired indazole product **6l** with complete retention of stereochemistry at the $\alpha$-position. This result suggests that isomerization of the imine intermediate does not occur under the reaction conditions, making the developed method very appealing with regard to asymmetric synthesis of 2*H*-indazoles substituted with $\alpha$-branched aliphatic groups. Interestingly, any exogenous hydrochloride salt was deleterious to the reaction; thus, the free bases of all amine coupling partners were required to obtain the desired indazole products.

Unfortunately, reactions with either glycine or alanine methyl ester failed to provide desired products (**6m,n**). Condensation of glycine methyl ester with *ortho*-nitrobenzaldehyde at elevated or room temperature led to a complex mixture of products. A similar result was observed with alanine methyl ester at elevated temperatures. However, clean imine formation with alanine methyl ester was observed when the condensation was conducted at room temperature over 12 h. Treatment of the resulting imine with tri-*n*-butylphosphine at 50 °C over 3 h resulted in complete consumption of the imine and no desired indazole. Using methyl $\alpha$-aminoisobutyrate in the one-pot procedure provided indazole **6o**, albeit in moderate yield, suggesting the increased acidity of the $\alpha$-imino proton is not tolerated under the cyclization conditions at the temperatures required for reduction.

In conclusion, a general method for the synthesis of a wide range of structurally diverse 2*H*-indazoles is presented. The use of tri-*n*-butylphosphine and protic solvent provided mild conditions for the reductive cyclization in a media compatible with imine formation. The optimized one-pot reaction improved the synthetic practicality of the transformation and enhanced the safety margin of the reaction by lowering the temperature profile and limiting the amount of reducing reagent compared to previous reports.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## ■ ASSOCIATED CONTENT

### Supporting Information

Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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