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**PAPER**

# One-pot synthesis of 1-alkyl-1*H*-indazoles from 1,1-dialkylhydrazones *via* aryne annulation†

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The reaction of readily accessible 1,1-dialkylhydrazones with commercially available *o*-(trimethylsilyl) aryl triflates provides a direct one-step route to pharmaceutically important 1-alkylindazoles. The products are obtained in high yields by one-pot NCS-chlorination/aryne annulation or $Ac_2O$-acylation/deprotection/aromatization protocols.

## Introduction

1*H*-Indazoles represent an important class of heterocyclic compounds that exhibit a wide range of biological and pharmaceutical activities,[1] including anti-inflammatory,[2] antitumor,[3] and anti-HIV[4] activity among others. Selected examples of 1-alkyl-1*H*-indazoles with notable pharmacological activities include granisetron, a serotonin 5-$HT_3$ receptor antagonist used to treat nausea and vomiting after chemotherapy;[5] lonidamine, used for the treatment of brain tumors;[6] and CL-958, an antitumor agent, which is currently in clinical evaluation (Fig. 1).[7]

Various methods for the synthesis of the 1*H*-indazole core have been developed.[8] However, most of them employ harsh reaction conditions, thus have limited the scope and applicability. Recently, several methodologies have been reported that involve aryne intermediates in [3 + 2] cycloaddition reactions with diazo compounds,[9] *N*-tosylhydrazones,[10,11] and *in situ* generated nitrile imines.[12] These methods afford 1*H*-indazoles, 1-acyl-1*H*-indazoles or 1-aryl-1*H*-indazoles under mild reaction conditions. However, no aryne-annulation approach to 1-alkyl-1*H*-indazoles has yet been reported.

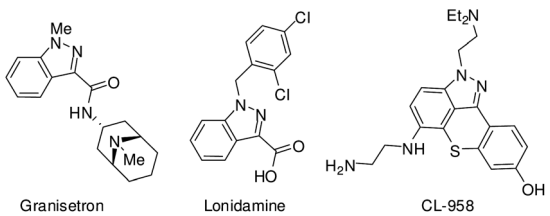


**Fig. 1** Biologically active 1-alkyl-1*H*-indazoles.

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†Electronic supplementary information (ESI) available: Experimental details for the preparation and characterization of starting materials and products; copies of $^1H$ and $^{13}C$ NMR spectra; copies of NOE spectra for the compound **15l**. See DOI: 10.1039/c2ob07117g

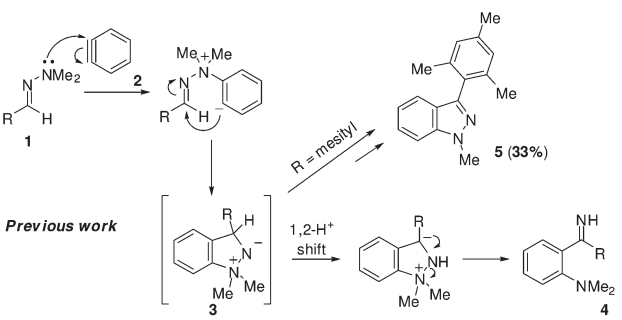
## Results and discussion

In our previous work, we have shown that the reaction of a variety of *N*,*N*-dialkylhydrazones with arynes seemingly proceeds through a cyclic intermediate **3** that subsequently undergoes ring opening to form the corresponding *o*-(dialkylamino) aryl imines **4** (Scheme 1).[13]

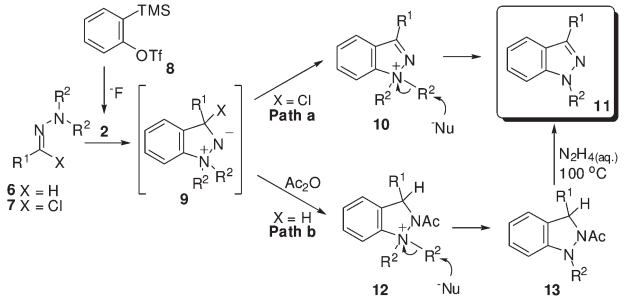
An unexpected result was obtained in the case of the mesityl-substituted substrate, where the corresponding indazole **5** was formed, albeit in only a 33% yield. In order to improve the scope and efficiency of this process, we envisioned that one can retain the cyclic nature of the intermediate **9** in two complementary ways (Scheme 2), namely by having a nearby leaving group (path a) or trapping the amide **9** with a trapping agent (path b).

To our delight, we found that the reaction of *N*,*N*-dimethylhydrazone chloride **7** ($R^1$ = Ph, $R^2$ = Me) with benzyne **2**, generated *in situ* from *o*-(trimethylsilyl)aryl triflate[14] **8** in presence of fluoride source, proceeds smoothly to afford indazole **11** in an 81% yield (Scheme 2, path a).

However, it did not prove to be efficient to purify and isolate the labile starting materials **7**. We promptly investigated the possibility of a one-pot procedure wherein the chlorine-containing hydrazones are not isolated, but generated *in situ* from 1,1-dialkylhydrazones **6** and NCS and further reacted with the *o*-(trimethylsilyl)aryl triflate **8** in the presence of a fluoride source.[15]




**Scheme 1**




Scheme 2

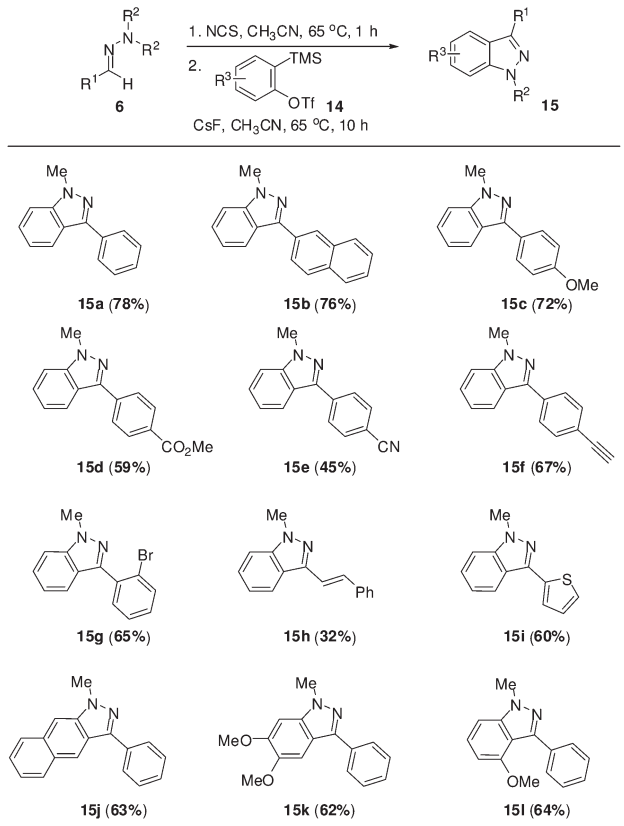
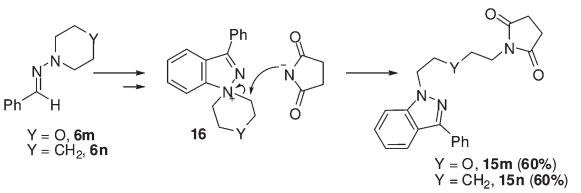



Chart 1




Scheme 3

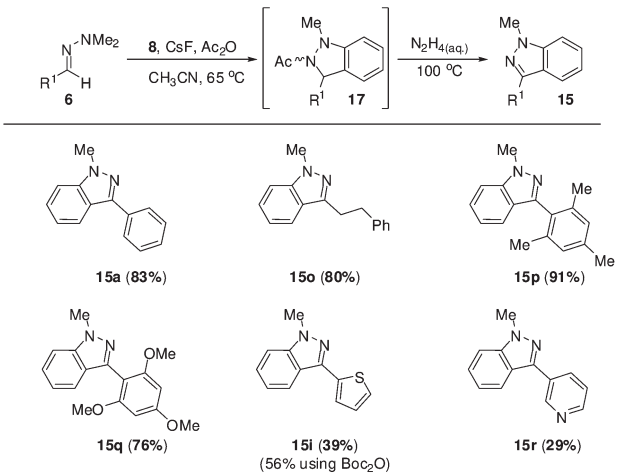



Chart 2

To our delight, the desired indazole **11** was obtained in a 78% yield. The optimal reaction conditions were found to be 1.1 equiv. of NCS per 1 equiv. of the hydrazone **6**, and a slight excess of the substrate **6** (1.2 equiv.) per 1 equiv. of the aryne precursor **8**. Both steps conveniently proceed in acetonitrile at 65 °C.

With the optimal conditions in hand, we next examined the scope and limitations of this method (Chart 1). A range of hydrazones was studied first. Aryl, alkenyl and heteroaryl hydrazones afforded the corresponding indazoles **15a–i** in 32–78% yields. Electron-poor aryl hydrazones afforded the corresponding indazoles **15d** and **15e** in lower yields (59 and 45%, respectively). The presence of a cyano group, terminal alkyne moiety, and an *ortho*-bromo substituent was tolerated under these reaction conditions. Unfortunately, hydrazones with $R^1$ = 4-nitrophenyl, 2-furyl, 2,3,5-trimethoxyphenyl and alkyl groups did not afford the desired indazoles, seemingly due to complications during the NCS chlorination step.

Other aryne precursors were also tested. Symmetrical naphthalyne and dimethoxybenzyne precursors afforded the desired indazoles **15j** and **15k** in good 63 and 62% yields, respectively. The unsymmetrical 3-methoxybenzyne precursor provided exclusively the 4-OMe regioisomer **15l** in a 64% yield.

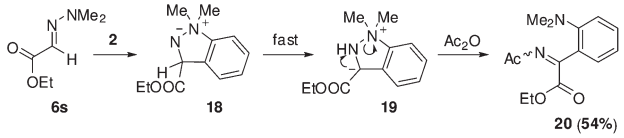
The structure of the product **15l** is consistent with the proposed mechanism (Scheme 2, path a).[16]

When cyclic hydrazones derived from *N*-aminopiperidine and *N*-aminomorpholine were employed in this one-pot process, the interesting products **15m** and **15n** were obtained, both in a 60% yield (Scheme 3). In these cases, the initially formed indazolium salt **16** undergoes ring-opening by the succinimide moiety present in the reaction media from the chlorination step.[17]

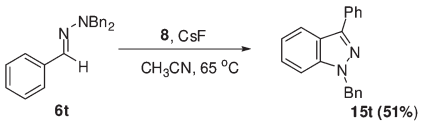
In order to overcome some limitations of the methodology using NCS, we also studied the reaction between the hydrazone **6a** ($R^1$ = Ph) and the benzyne precursor **8** in the presence of acetic anhydride (Scheme 2, path b). We were pleased to observe formation of the corresponding trapped product **17a** ($R^1$ = Ph) in an 83% yield, which could also be subsequently deacetylated and aromatized *in situ* to produce the indazole **15a** (overall yield for the 2 steps of 63%). After some optimization studies, we were able to obtain the latter in an 83% overall yield without isolating the intermediate product **17a**. The scope of this process is summarized in Chart 2.

Gratifyingly, a variety of substituents in the $R^1$ position of the hydrazone are well tolerated. For example, the product **15o** is obtained in an 80% yield. The electron-rich hydrazones, that failed to react efficiently under our NCS-mediated protocol, have afforded the corresponding indazoles **15p** and **15q** in excellent




**Scheme 4**




**Scheme 5**

yields (91 and 76%), despite their steric encumbrance. On the other hand, electron-deficient hydrazones, such as 2-thiophenyl and 3-pyridyl hydrazones, provide the corresponding products **15i** and **15r** in only 39 and 29% yields, respectively. In the case of a stronger electron-withdrawing $CO_2Et$ group, *N*-acyl imine **20** was isolated in a 54% yield, instead of the desired indazole (Scheme 4). This result can be rationalized by considering the proposed intermediate **18**, in which the acidic C-3 hydrogen can be easily transferred to the negatively charged nitrogen atom. Subsequent ring-opening results in formation of the product **20**.

Alternatively, $Boc_2O$ has been tested as a trapping source (with subsequent deprotection with aqueous HCl), but in most cases similar or lower yields of the indazoles have been obtained, except for the 2-thiophenyl product **15i**, for which the yield improved from 39 to 56%.

Surprisingly, *N*,*N*-dibenzyl-substituted hydrazone **6t** provided the corresponding indazole **15t** with neither a trapping agent nor NCS employed (Scheme 5). The product was isolated in a higher (51%) yield when a two fold-excess of the benzyne precursor **8** was used. All attempts to obtain this indazole through the optimized NCS or $Ac_2O$ routes have so far proved to be inferior to the one described above.

## Conclusion

In summary, 1-alkyl-1*H*-indazoles can be prepared from arynes and hydrazones in high yields by one-pot NCS-chlorination/aryne annulation or $Ac_2O$-acylation/deprotection protocols. This chemistry provides a convenient route to 1-alkyl-1*H*-indazoles from readily available *N*,*N*-dimethylhydrazones and presents a valuable extension of the known synthetic routes to indazoles.

## Experimental

The $^1H$ and $^{13}C$ NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz, respectively. Chemical shifts are reported in $\delta$ units (ppm) by assigning the TMS resonance in the $^1H$ NMR spectrum as 0.00 ppm and the $CDCl_3$ resonance in the $^{13}C$ NMR spectrum as 77.23 ppm. All coupling constants (*J*) are reported in Hertz (Hz). All commercial reagents were used directly as obtained. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All melting points were obtained using an EZ-Melt automated melting point apparatus and are uncorrected. High resolution mass spectra (HRMS) were obtained using an Agilent QTOF 6540 mass spectrometer (ESI at a voltage of 70 eV). All mass spectra (MS) were obtained using a GCT-Agilent 6890 gas chromatograph/mass spectrometer (EI at a voltage of 70 eV). All IR spectra were obtained using a Nicolet 380 FT-IR apparatus.

### General procedure for the preparation of indazoles 15 by a one-pot NCS procedure [1-methyl-3-phenyl-1*H*-indazole[18] (15a) as an example]

To a solution of benzaldehyde dimethylhydrazone **6a** (46 mg, 0.31 mmol, 1.25 equiv.) in 1 mL of acetonitrile under an inert atmosphere *N*-chlorosuccinimide (46 mg, 0.34 mmol, 1.38 equiv.) was added and the reaction mixture was stirred for 1 h at 65 °C. Then an additional 4 mL of acetonitrile, together with CsF (114 mg, 0.75 mmol, 3 equiv.) and *o*-(trimethylsilyl)phenyl triflate (61 μL, 0.25 mmol, 1.0 equiv.) were added and the reaction mixture was stirred at 65 °C for an additional 10 h (monitored by TLC). After cooling to room temperature, the reaction mixture was filtered through a short column of Celite and concentrated under vacuum. The crude reaction mixture was subjected to column chromatography using ethyl acetate–hexanes (1 : 10) as eluent and afforded 40.6 mg (78%) of product **15a**, gray solid: M.P. 81–83 °C; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.13 (s, 3H), 7.21 (s, 1H), 7.42 (t, $J$ = 4.3 Hz, 3H), 7.52 (t, $J$ = 7.6 Hz, 2H), 7.99 (d, $J$ = 8.3 Hz, 2H), 8.04 (d, $J$ = 8.2 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 35.72, 109.38, 121.09, 121.53, 121.81, 126.45, 127.57, 127.99, 128.98, 133.89, 141.63, 143.91; MS (EI) *m*/*z* (%) 208 ($M^+$, 100%), 77 (10%); HRMS (EI) calcd for $[M + H]^+$ $C_{14}H_{13}N_2$ 209.1073, found 209.1075; IR ($CH_2Cl_2$, $cm^{-1}$) 2939 (m), 1617 (s), 1495 (s), 1351 (s).

### General procedure for the one-pot synthesis of indazoles 15

**Method A ($Ac_2O$–$N_2H_4$) [1-methyl-3-phenyl-1*H*-indazole (15a) as an example].** To a mixture of benzaldehyde dimethylhydrazone **6a** (37 mg, 0.25 mmol), CsF (114 mg, 0.75 mmol, 3 equiv.), acetic anhydride (47 μL, 0.50 mmol, 2 equiv.) and 5 mL of acetonitrile in a 10 mL vial, *o*-(trimethylsilyl)phenyl triflate (84 mg, 0.28 mmol, 1.1 equiv.) was added. The vial was capped and the reaction mixture was allowed to stir for 10 h at 65 °C. Then the solvent was evaporated under reduced pressure, 3 mL of $N_2H_4 \cdot H_2O$ (85% solution, w/w) was added and the mixture was heated at 100 °C for an additional 10 h. After cooling to room temperature, 25 mL of dichloromethane was added to the residue, and the reaction mixture was poured into 50 mL of water in a separatory funnel. After shaking the layers, the organic fraction was separated and the aqueous layer was extracted with dichloromethane (2 × 15 mL). All organic fractions were combined and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes–EtOAc as the eluent to afford the desired indazole **15a** in an 83% yield.

**Method B ($Boc_2O$–HCl) [1-methyl-3-phenethyl-1*H*-indazole (15o) as an example].** To a mixture of dihydrocinnamaldehyde dimethylhydrazone **6o** (44 mg, 0.25 mmol), CsF (114 mg,

0.75 mmol, 3 equiv.), di-*tert*-butyl dicarbonate (344 μL, 1.50 mmol, 6 equiv.) and 5 mL of acetonitrile in a 10 mL vial, *o*-(trimethylsilyl)phenyl triflate (84 mg, 0.28 mmol, 1.1 equiv.) was added. The vial was capped and the reaction mixture was allowed to stir for 10 h at 65 °C. Then 3 mL of 1 M HCl was added and the mixture was heated at 75 °C for an additional 3 h. After cooling to room temperature, 25 mL of dichloromethane was added to the residue, and the reaction mixture was poured into 25 mL of water in a separatory funnel. After shaking the layers, the organic fraction was separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). All organic fractions were combined and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes–EtOAc as the eluent to afford the desired indazole **15o** as a colorless amorphous solid in an 81% (method A: 80%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.15 (dd, $J$ = 10.2, 6.2 Hz, 2H), 3.30 (dd, $J$ = 10.1, 6.1 Hz, 2H), 4.04 (s, 3H), 7.12 (t, $J$ = 7.6 Hz, 1H), 7.20–7.26 (m, 1H), 7.28–7.50 (m, 6H), 7.63 (d, $J$ = 8.1 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 29.47, 35.36, 35.96, 109.04, 117.54, 119.81, 120.47, 122.81, 126.18, 126.35, 128.59, 140.98, 142.00, 144.80; MS (EI) *m*/*z* (%) 236 ($M^+$, 58%), 145 (100%), 91 (21%); HRMS (EI) calcd for $[M + H]^+$ $C_{16}H_{17}N_2$ 237.1386, found 237.1393; IR ($CH_2Cl_2$, $cm^{-1}$) 2928 (s), 2859 (m), 1616 (s), 1505 (s).

## Acknowledgements

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