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New Synthesis of 1-Substituted-1*H*-indazoles via 1,3-Dipolar Cycloaddition of *in situ* Generated Nitrile Imines and Benzyne

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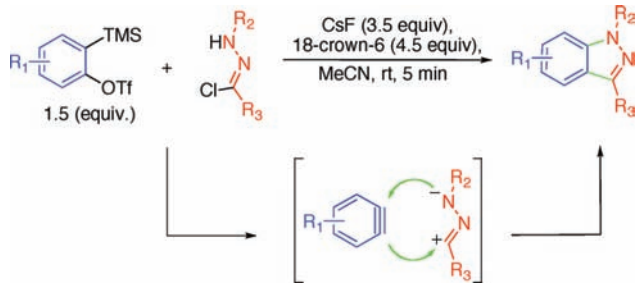
ABSTRACT



A new synthesis of 1-substitued-1*H*-indazoles via 1,3-dipolar cycloaddition of nitrile imines to benzyne is described. The reaction is completed within 5 min, affording the corresponding N(1)−C(3) disubstituted indazoles in moderate to excellent yields.

1*H*-Indazoles are a pharmaceutically important class of nitrogen-containing heterocycles that show a broad range of pharmacological activity including anti-HIV,[1] Rho-kinase inhibition,[2] anti-inflammatory,[3] antitumor,[4] cardiovascular,[5] and antinociceptive activity,[6] among others. Their desirable properites render them attractive targets for drug discovery,[7] and as such, numerous syntheses of the indazole core have been described.[8] One general route involves the diazotisation of *o*-methyl substituted anilines follwed by base promoted cyclization.[9] Other intramolecular cyclizations are also possible.[10−17] For instance, 1-aryl-1*H*-indazoles can be

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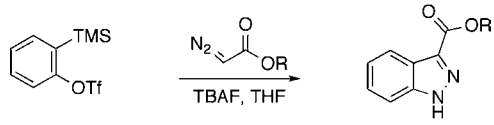
synthesized via Pd catalyzed ring closure of *N*-aryl-*N*′-(*o*-bromobenzyl)hydrazines, [*N*-aryl-*N*′-(*o*-bromobenzyl)-hydrazinato-*N*′]-triphenylphosphonium bromides,[10] substituted *o*-bromobenzaldehyde arylhydrazones,[11] substituted *o*-bromoacetophenone arylhydrazones[11b] and hydrazones.[12] An alternative route involves condensation of hydrazine to *o*-halo[13] or *o*-alkoxy arylhydrazone,[14] and more recently, copper[15,16] catalysis has been used for the intramolecular amination of *o*-haloarylcarbonylic compounds. There are however disadvantages of using such protocols such as limitation of substrate choice, elevated temperatures, and the requirement for metal mediated catalysis. An improved intramolecular cyclization was recently reported by Stambuli *et al.*,[17] where mild conditions for the cyclization of *o*-aminobenzoximes were developed, for selective oxime activation, affording both 1*H*-indazoles and substitued-1*H*-indazoles in good yield.

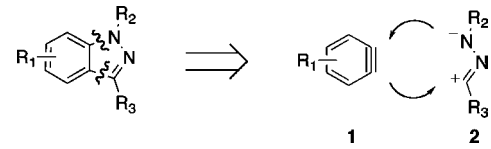
Scheme 1. Synthesis of 1*H*-Indazoles via [3 + 2] Cycloaddition



1,3-Dipolar cycloadditions of diazomethane derivatives with benzyne offer an alternative route to 1*H*-indazoles (Scheme 1). The first example was reported by Huisgen and Knorr in 1961,[18] and recent developments have been described by the groups of Yamamoto (2007)[19] and Larock (2008).[20] The latter methods gave 1*H*-indazoles in good yields under very mild conditions. Even so, these protocols were restricted to substrates bearing an ester group at the 3-position, limiting the diversity of the corresponding 1*H*-indazole product. Consequently, we felt it desirable to develop a protocol to access highly decorated *N*(1)−*C*(3) disubstituted indazoles.

Recently, we have had considerable success employing benzyne (**1**) in 1,3-dipolar cycloaddition reactions in the syntheses of 1,2-benzisoxazoles[21] and benzotriazoles.[22] We were keen to build upon our expertise in this area, and herein

Scheme 2. Schematic Hypothesis: 1,3-Dipolar Cycloaddition of Benzyne (**1**) and Nitrile Imines (**2**)



describe our studies on the development of a new route to 1-substituted-1*H*-indazoles using nitrile imines (**2**) as 1,3-dipoles (Scheme 2).

Nitrile imines have been used extensively as 1,3-dipoles in [3 + 2] cycloaddition reactions with alkynes yet, to the best of our knowledge, have not been reported with benzyne (**1**). The absence of literature precedence may be attributed to the difficulty associated in forcing two highly unstable intermediates to react preferentially with one another. In any event, it presented a unique opportunity for us to exploit this untapped transformation. Benzyne is well-known to undergo self-dimerization to give biphenylene,[23] whereas nitrile imines can undergo [3 + 3] self-cycloaddition,[24] fragmentation into nitriles,[25] rearrangement into carbodiimides or azirnes,[26] and intramolecular cyclizations.[27]

Nitrile imines (**2**) are usually generated *in situ* by a base-induced dehydrodechlorination of hydrozonyl chlorides,[24,28] whereas arynes are easily accessible *in situ*, from *o*-(trimethylsilyl)aryl triflates under very mild conditions.[29] In our work on 1,2-benzisoxazole chemistry, we demonstrated that TBAF could mediate the *in situ* generation of both benzyne (**1**) and nitrile oxides simultaneously[21a] and were keen to determine if **1** and **2** could be obtained under analogous conditions. Our studies began using *o*-(trimethylsilyl)phenyl triflate (**3**) as the benzyne precursor and phenylbenzenecarbohydrazonoyl chloride (**4**) as a source of nitrile imine (Table 1).

A variety of conditions were screened, varying fluoride source, molar ratios, substrate concentrations, temperature, and polar media (Table 1). Gratifyingly, all tested conditions gave the target disubstituted-1*H*-indazole, 1,3-diphenyl-1*H*-indazole (**5**) in varying yields. Using the strongly nucleophilc fluoride source TBAF, the target indazole could only be obtained in moderate yield (entries 1−4, Table 1). In each case, a competing self-dimerization of the nitrile imine into

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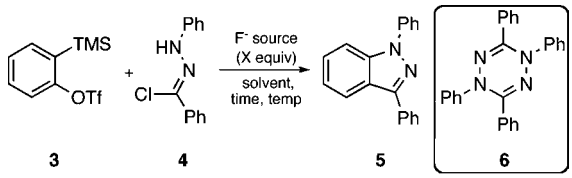
Table 1. Preliminary Screening and Optimizaton



entry[a]	"F⁻" source/base	equiv	solvent	temp [°C]	time[b]	yield [%][c]
1[d]	TBAF	2.5	THF	rt	5 min	58
2[d]	TBAF	2.5	THF	0	10 min	67
3[e]	TBAF	2.5	THF	rt	5 min	63
4[e]	TBAF	2.5	MeCN	rt	5 min	38
5[e]	CsF	2.5	MeCN	rt	24 h	trace
6[e]	KF/18-C-6	2.5:2.7	MeCN	rt	5 min	72
7[e]	CsF/18-C-6	2.5:2.7	MeCN	rt	5 min	79
8[e]	CsF/18-C-6	2.5:2.7	THF	rt	5 min	62
9[e]	***CsF/18-C-6***	***3.5:4.5***	***MeCN***	***rt***	***5 min***	***99***
10[e]	CsF/18-C-6	3.5:4.5	THF	rt	5 min	81

[a] Reaction performed on 0.433 mmol of **4** (100 mg) using 1.5 equiv of **3** (0.158 mL, 0.65 mmol). [b] Reaction monitored by LCMS until **4** was consumed. [c] Isolated yield. [d] Reaction performed in 0.46 mL of solvent. [e] Performed in 1.5 mL of solvent.

the corresponding dihydrotetrazine derivative, 1,3,4,6-tetraphenyl-1,4-dihydro-(1,2,4,5)tetrazine (**6**) was apparent. Several modifications of the reaction conditions were attempted to solve this issue. Addition of TBAF to a solution of **3** and **4** in THF at room temperature gave **5** in 58% (entry 1, Table 1), whereas addition under ice-cold conditions gave an increased yield of 67% (entry 2, Table 1). It was evident that the rate of formation of **1** was not equal to that of **2**, resulting in undesirable side reactions predominating over the formation of 1,3-diphenyl-1*H*-indazole (**5**). Diluting the reaction mixture by 3-fold did not offer any beneficial effect (entry 3, Table 1), whereas shifting to a more polar solvent, MeCN, gave significantly reduced yield (38%, entry 4, Table 1).

Switching the fluoride source to CsF furnished **5** in trace amount (entry 5, Table 1). Interestingly, and in agreement with a recent report by Ferringa et al.,[3] when KF or CsF were used in conjunciton with 18-crown-6 (18-C-6), better results were achieved (72−99%, entries, 6−10, Table 1). It was found that both molar ratio of CsF/18-crown-6 and solvent polarity had a significant effect on product formation (entries 7−10, Table 1). The use of 18-crown-6 drastically increased the rate of formation of both benzyne (**1**) and nitrile imine (**2**), and it was possible to equilibrate their generation by changing the equivalence of 18-crown-6. Optimal results were obtained using CsF/18-crown-6 [3.5:4.5 equiv] in MeCN at room temperature with a reaction time of 5 min (entry 9, Table 1).[30]

With these optimized conditions in hand, we were keen to investigate the substrate scope (Table 2). The protocol

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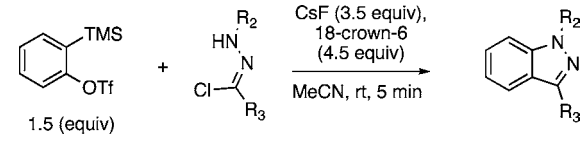
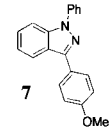
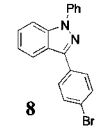
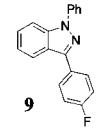
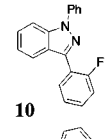
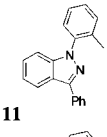
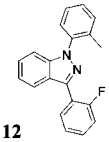
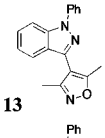
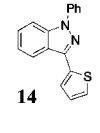
Table 2. Scope of the Reaction



entry[a]	product	yield [%][b]
1	 **7**	60
2	 **8**	79
3	 **9**	60
4	 **10**	49
5	 **11**	70
6	 **12**	59
7	 **13**	66
8	 **14**	60

[a] Reaction performed on 0.433 mmol of hydrazonoyl chlorides. [b] Isolated yield.

was found to tolerate a range of functionalities, including aryl and heterocyclic substituted hydrozonyl chlorides (entries 1−8, Table 2). Hydrozonyl chlorides bearing heterocycles, such as thiophene and isoxazole were also well tolerated (entries 7 and 8, Table 2), giving **13** and **14** in 66% and 60% respectively. The electronic properties of the nitrile imine substituents affected the efficiency of the reaction, with electron poor fluoride substrates leading to reduced yields.

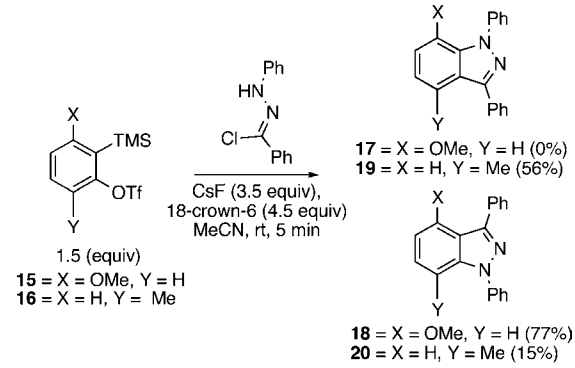
Nitrile imines generated from aryl hydrozonyl chlorides bearing electron-donating groups, or electron-withdrawing groups, were found to self-dimerize preferentially, thus leading to lower yields (entries 3, 4 and 6, Table 2). Although electronics are clearly important, sterics may also play a key

role in determening which pathway the nitrile imine follows. Generally, sterically hindered nitrile imines[21] are longer lived speices in solution and dimerize at a slower rate. On the other hand, this stabilizing steric effect may also slow down or encumber the reactivity of the 1,3-dipole with benzyne, thus allowing the reactive aryne to undergo alternative reaction pathways. Thus, it is clear that several factors are crucial when finetuning the reactivity, highlighting the problems associated with generating two highly reactive intermediates simultaneously.

To gain insight into the regiochemical effects that substituents on benzyne may have, studies were performed with the benzyne precursors, 3-(methoxy)-2-(trimethylsilyl)phenyl triflate (**15**) and 2-methyl-6-(trimethylsilyl)phenyl triflate (**16**), in conjunction with substrate **4** under the optimized conditions. The results are illutrsated in Scheme 3. Interestingly, the reaction carried out using **15** afforded a single regioisomer **18** in 77%, whereas **16** gave a mixture of **19**:**20** in a ratio of 3.0:0.8 [^{1}H NMR] (56 and 15% yield, respectively, Scheme 3). The difference in regio-control observed for **15** and **16** was attributed to a more pronounced electronic effect exerted by the methoxy group on **15** as compared to the methyl substituent.[31]

In summary, we have demonstrated for the first time that 1-substituted-1*H*-indazoles can be prepared by a [3 + 2] cycloaddition between *in situ* generated nitrile imines and arynes using CsF/18-crown-6. The reaction is complete within 5 min, affording the disubstituted compounds in good yields. This unprecedented reaction complements existing methodologies to 1*H*-indazoles, offering a convergent and rapid access to this important motif. We believe this modular protocol will find wide use in drug discovery applications and in the synthesis of chemical arrays.

Scheme 3. Synthesis of Substituted 1*H*-Indazoles via [3 + 2] Cycloaddition



Acknowledgment. J.E.M. thanks EPSRC, GSK, and The University of Nottingham for financial support.

Supporting Information Available: Full characterization data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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