Efficient and Convenient Synthesis of Indazol-3(2*H*)-ones and 2-Aminobenzonitriles

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A mild, efficient, one-pot protocol for the synthesis of indazole-3(2*H*)-ones via cyclization of nitro-aryl substrates through low-valent titanium reagent has been described. The method used Triethylamine (TEA) to control pH. Particularly, 2-aminobenzonitriles were synthesized by one step easily. The mechanistic course of the reaction suggests the involvement of an anion leading to an intramolecular cyclization via N−N bond formation.

Introduction

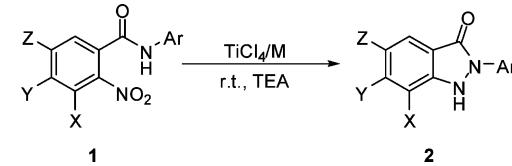
Seven of the top ten selling drugs are nitrogen-containing heterocycles,[1] and these structural motifs are also found in many natural products.[2] In this context, chemists have developed an array of methods for the construction of these important heterocycles.[3] However, there is a plethora of tools available for carbon−heteroatom bond formation, but the field of heteroatom−heteroatom bond formation remains comparatively less developed.

Because several indazolone derivatives have gained noteworthy importance in view of their promising pharmacological properties, such as anti-inflammatory,[4] antipsychotic,[5] or antihyperlipidemic agents,[6] we decided to focus on the synthesis of indazol-3(2*H*)-one derivatives. The most widely used routes to these compounds are the high pressure transition metal catalyzed carbonylation of azobenzenes,[7] the cyclization of *o*-arylhydrazinobenzoic acids,[8] the isomerization of 3-aryl-2-hydroxyindazoles,[9] and the base catalyzed cyclization of *o*-azidobenzanilides.[10] However, all of these routes entail multiple steps from commercially available precursors and in some instances necessitate access to specialized equipment or the use of potentially hazardous intermediates.

A recent report details the preparation of *N*,*N*′-disubstituted indazolone derivatives mediated by hypervalent iodine reagent PIFA;[11] however, the reaction temperature (0 °C) limited the application of this method. Peters et al. reported exploiting nucleophilicity of the azo group for cyclization to indazole derivatives, 2-phenyl-1,2-dihydroindazol-3-one was obtained unexpected, and only this kind of indazolone was synthesized.[12] The Chen group claimed that *o*-nitrosobenzaldehyde reacts with benzylamine in $CHCl_3$ at room temperature to yield 3-benzylamino-2,1-benzisoxazole;[13] however, the Kurth group repeated the work and claimed 2,1-benzisoxazoles are indazolones[14] and the reaction time (5 h) also limited the application of the method. 2-Arylindazolones were obtained from the reduction of *o*-nitrobenzanilide with zinc and sodium hydroxide;[15] however, the reaction time is too long (15 h), the yield of the product is low (only 11%−51%), and many are lower than 40%. 2,3-Dihydrooxazolo[3,2-*b*]indazole has been synthesized and utilized to provide easy access to 1*H*-indazolones.[16] However, none of the compounds prepared by the above methods contained 5-, 6-, and 7- substituents. Therefore, a novel and general approach would be desirable and of high value.

Low-valent titanium reagents have exceedingly high ability to promote reductive coupling of carbonyl compounds, nitro-compounds, and cyano-group compounds and are attracting increasing interest in organic synthesis.[17] We have previously reported the cyclodimerization of α,β-unsaturated ketones and α,β-unsaturated nitriles promoted by this reagent yielding functional cyclopentanes[18] and cyclopentenes,[19] respectively. Recently, we reported the synthesis of quinazolinones, quinazoline-2,4-diones, imidazo[1,2-*c*]quinazolines, imidazo[1,2-*c*] quinazolinones, and 2-thioxoquinazolinones by the reaction of nitro-compounds with orthoformates, triphosgene, aldehydes, ketones, and isothiocyanates, respectively, induced by a low-valent titanium reagent.[20] However, most of the reported reactions mediated by a low-valent titanium reagent have been carried out in the presence of no base. Quite surpringsly, base controlled reactions with low-valent titanium reagents have not stimulated much interest so far. In this paper, we would like to report a novel and convenient Triethylamine (TEA)-controlled protocol for the synthesis of the indazolone skeleton via a low-valent titanium reagent (Scheme 1).

Scheme 1. Synthesis of Indazolone **2**



1 **2**

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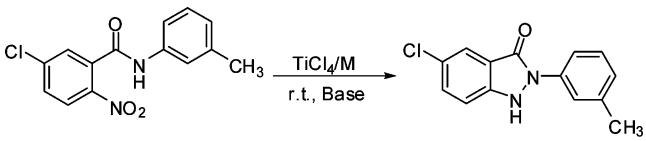
Table 1. Selected Assays Performed on 5-Chloro-2-nitro-*N*-*m*-tolylbenzamide **1a**



1a **2a**

entry	$TiCl_4$/M	base/pH	yield/%
1	$TiCl_4$/Zn	TEA/8	0
2	$TiCl_4$/Mg	TEA/8	0
3	$TiCl_4$/Al	TEA/8	0
4	$TiCl_4$/Fe	TEA/8	63
5	$TiCl_4$/Fe	no base/2	0
6	$TiCl_4$/Fe	TEA/7	35
7	$TiCl_4$/Fe	TEA/9	36
8	$TiCl_4$/Fe	TEA/10	32
9	$TiCl_4$/Fe	pyridine/8	15
10	$TiCl_4$/Fe	pyridine + TEA/8	38

On the basis of our previous experience, we selected 5-chloro-2-nitro-*N*-*m*-tolylbenzamide **1a** as a model system to optimize the experimental conditions for the proposed cyclization step.

As shown in Table 1, we briefly examined the effect of different low-valent titanium reagents and pH in low-valent titanium reagents on the success of the cyclization step.

When compound **1a** was reduced by $TiCl_4$/Fe and no base was added, no desired product **2a** was obtained (entry 5, Table 1). When compound **1a** was reduced with different low-valent titanium reagents in TEA and pH = 8 (entries 1−4, Table 1), only $TiCl_4$/Fe can give the desired product **2a** (63% yield). To further optimize reaction conditions, a similar test was carried out at pH ranging from 7 to 10 with an increment of 1 each time. The yield of product **2a** was increased as pH was increased from 7 to 8 (entries 4 and 6, Table 1). However, a further increase of pH to 9 and 10 failed to improve the yield of product **2a** (entries 7 and 8, Table 1). Moreover, we also tested other bases such as pyridine (entries 9 and 10, Table 1); however, the yields were low (15% and 38%). Therefore, TEA and pH = 8 was chosen as the reaction condition for all further reactions.

Having established an optimal protocol for the projected process, we then performed the reaction of a variety of *N*-aryl-*o*-nitrobenzamides **1** via low-valent titanium reagent ($TiCl_4$/Fe) at pH = 8. The results are summarized in Table 2.

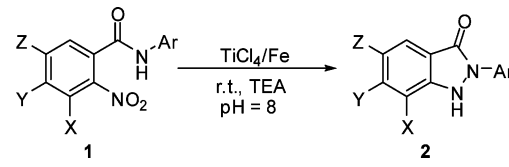
As shown in Table 2, it can be seen that the proposed cyclization process proved to be suitable for substrates in which the amine functionality was substituted by not only aryl groups with either electron-withdrawing groups (such as halide groups) or electron-donating groups (such as alkyl groups) but also to heterocyclic groups under the same conditions. The yields of heterocyclic amines were superior to those of aryl-substituted ones. No remarkable steric hindrance on the reaction was observed, for example, the desired product **2i** was obtained in 72% yield when amine was quinolin-6-amine.

In order to demonstrate the efficiency and the applicability of the present method, we performed the cyclization of a variety of *N*-alkyl-*o*-nitrobenzamide under the optimized conditions. However, the desired product indazolone **2** can not be obtained, *o*-aminobenzamide **3** was obtained (Scheme 4, Table 3). Therefore, the effectiveness for the cyclization to indazolone proved to be restricted to *N*-arylamides.

During our research, 2-aminobenzonitrile **4** was obtained in excellent yield when R = H and alkalinity increased (Scheme 5, Table 4).

2-Aminobenzonitriles can be prepared by multistep reactions using ethyl 2-aminobenzoate, NH_3, Trifluoro acetic anhydride (TFAA), potassium carbonate, and TEA as raw materials.[21] Kreimeyer[22] reported the synthesis of 2-nitrobenzonitrile using 2-nitrobenzamide as raw material, then 2-nitrobenzonitrile was reduced by $TiCl_3$ to

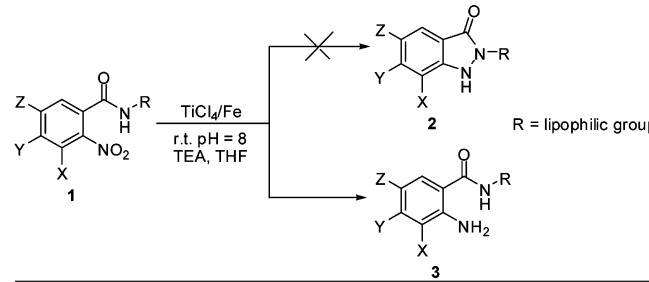
Table 2. Cyclization of *N*-Aryl-*o*-nitrobenzamides **1**



1 **2**

entry	product	X	Y	Z	Ar	time/min	yield/%
1	**2a**	H	H	Cl	3-$CH_3C_6H_4$	15	63
2	**2b**	H	H	Cl	4-$CH_3C_6H_4$	15	55
3	**2c**	H	Cl	H	3-Cl-4-$CH_3C_6H_3$	20	69
4	**2d**	H	Cl	H	4-FC_6H_4	8	74
5	**2e**	H	Cl	H	4-BrC_6H_4	5	78
6	**2f**	H	H	H	2-pyridyl	10	75
7	**2g**	H	Cl	H	2-pyridyl	10	79
8	**2h**	H	H	Cl	2-pyridyl	12	82
9	**2i**	H	H	Cl	quinolin-6-yl	30	72
10	**2j**	CH_3	H	H	2-pyridyl	15	51

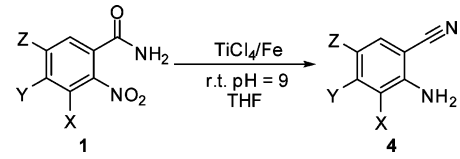
Table 3. Synthesis of *N*-Alkyl-2-aminobenzamides



1 **2** **3**

entry	product	X	Y	Z	R	time (min)	yield (%)
1	**3a**	H	H	H	*n*-octyl	5	95
2	**3b**	H	H	H	4-$FC_6H_4CH_2$	5	92
3	**3c**	H	H	H	$C_6H_5CH_2$	4	94
4	**3d**	H	Cl	H	$C_6H_5CH_2$	4	96
5	**3e**	H	H	Cl	*n*-butyl	4	93
6	**3f**	CH_3	H	H	$C_6H_5CH_2$	5	97

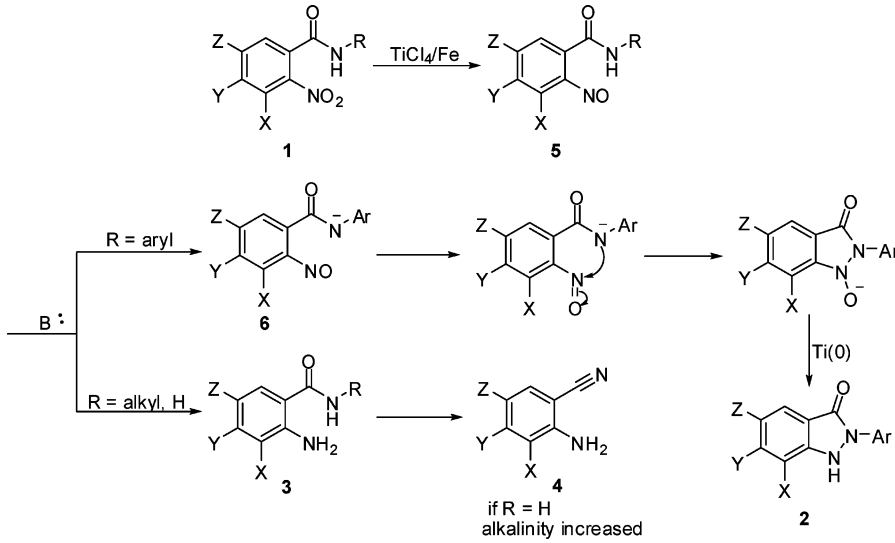
Table 4. Synthesis of 2-Aminobenzonitrile



1 **4**

entry	product	X	Y	Z	time/min	yield/%
1	**4a**	H	Cl	H	2	93
2	**4b**	H	H	Cl	2	83
3	**4c**	CH_3	H	H	3	74

Scheme 2. Reaction Mechanism



2-aminobenzonitrile; this method also suffers from some disadvantages, such as drastic conditions, complex manipulation and two-step reactions. To our surprise, as shown in Table 4, we found that the reaction time of our method is very fast, only 2−3 min, and the yields are very high; therefore, we also have developed an efficient and convenient method for the preparation of 2-aminobenzonitrile.

A proposed mechanism is outlined in Scheme 2. $TiCl_4$ is reduced by Fe dust to give low-valent titanium species. In the initial step, **1** was reduced by low-valent titanium reagent to nitroso-compound **5**. To *N*-arylamides, R = aryl, anion **6** formed in the presence of alkali TEA. So the anion attacked −N=O, and product indazolone **2** was then obtained. However, when R = alkyl or H, because TEA is a weak base and anion can not be formed, nitroso was then reduced to amino further, so 2-alkyl-1*H*-indazol-3(2*H*)-ones cannot be obtained and 2-aminobenzamides were obtained instead. If R = H and alkalinity increased, 2-aminobenzamides were reduced to 2-aminobenzonitriles by low-valent titanium reagent.

The structures of all the synthesized compounds were established on the basis of their spectroscopic data. The structure of **2h** was further confirmed by X-ray diffraction analysis. The molecular structures of the product **2h** is shown in Figure 1.

Conclusion

In conclusion, the easy-to-handle starting material, short reaction time, and simple reaction conditions have been employed satisfactorily in the preparation of a series of 2-aryl substituted indazolones. Meanwhile, a novel method for the synthesis of 2-aminobenzonitrile was found. Our approach features the first successful cyclization of *N*-aryl-*o*-nitrobenzamides by controlling pH of a low-valent titanium reagent. Therefore, a novel method for the construction of new N−N linkages was found, hence offering easy access to a diverse array of *N*-heterocyclic compounds.

Experiment Section

General. Tetrahydrofuran (THF) was distilled from sodium-benzophenone immediately prior to use. The analytically pure iron powder (200 meshes) was inactivated at all. All reactions were conducted under N_2 atmosphere. Melting points are uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in cm^{-1}. ^1H NMR was determined on NMRststem-300 MHz spectrometer in DMSO-d_6 or $CDCl_3$ solution. *J* values are in hertz. Chemical shifts are expressed in parts per million downfield from internal standard trimethylsilane (TMS). X-ray diffractions were recorded on a Siemens P4 diffractometer.

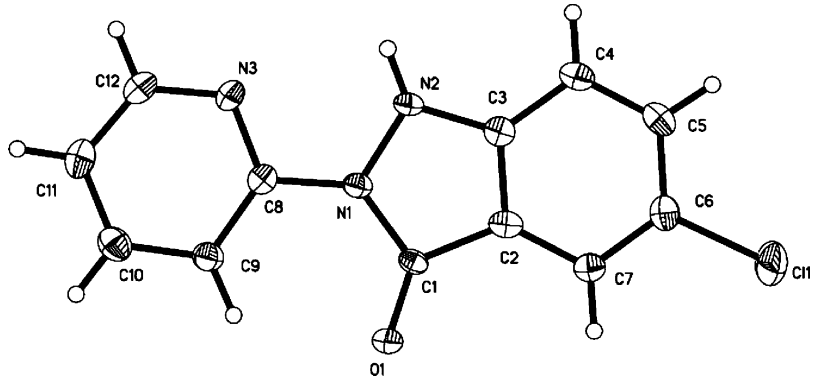


Figure 1. Crystal structure of product **2h**.

General Procedure for the Synthesis of Indazol-3(2*H*)-ones (2). $TiCl_4$ (0.5 mL, 5 mmol) was added dropwise using a syringe to a stirred suspension of iron powder (0.56 g, 10 mmol) in freshly distilled anhydrous THF (10 mL) at room temperature (rt) under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to rt, and then, 7 mL TEA was added; the pH was about 8. A solution of *N*-aryl-*o*-nitrobenzamides (1 mmol) in THF (3 mL) was added dropwise. The reaction mixture was then refluxed for 8−20 min under N_2. After this period, the thin layer chromatography (TLC) analysis of the mixture showed the reaction to be complete. The reaction mixture was quenched with 5% HCl (15 mL) and extracted with $CHCl_3$ (3 × 40 mL). The combined extracts were washed with water (3 × 40 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by recrystallization from 95% ethanol.

6-Chloro-2-(4-fluorophenyl)-1*H*-indazol-3(2*H*)-one (Entry 4, Table 2). Red solid (74% yield). mp 236−238 °C. IR (KBr) ν: 3122, 1648, 1621, 1510, 1412, 1437, 1346, 1317, 1230, 1063, 937, 828, 798 cm^{-1}, ^1H NMR (300 MHz, DMSO-d_6) δ 7.20 (d, J = 8.4 Hz, 1H, ArH), 7.36 (t, J = 9.0 Hz, 2H, ArH), 7.46 (s, 1H, ArH), 7.75 (d, J = 5.4 Hz, 1H, ArH), 7.86−7.90 (m, 2H, ArH), 11.00 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 114.37, 114.99, 115.61, 115.80, 115.90, 123.08, 123.18, 131.20, 137.32, 151.73, 167.58. HRMS found: m/z 262.0309 (M^+), calcd for $C_{13}H_8N_2O^{35}ClF$: M, 262.0309.

General Procedure for the Synthesis of *o*-Aminobenzamides (3). $TiCl_4$ (0.5 mL, 5 mmol) was added dropwise using a syringe to a stirred suspension of iron powder (0.56 g, 10 mmol) in freshly distilled anhydrous THF (10 mL) at rt under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to rt, and then, 7 mL TEA was added; the pH was about 8. A solution of *N*-alyl-*o*-nitrobenzamides (1 mmol) in THF (3 mL) was added dropwise. The reaction mixture was then refluxed for about 5 min under N_2. After this period, the TLC analysis of the mixture showed the reaction to be complete. The reaction mixture was quenched with 5% HCl (15 mL) and extracted with $CHCl_3$ (3 × 40 mL). The combined extracts were washed with water (3 × 40 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product **3** was purified by recrystallization from 95% ethanol.

2-Amino-*N*-octylbenzamide (Entry 1, Table 3). White solid (95% yield). mp 65−66 °C (literature value[23] 66−67 °C). IR (KBr) ν: 3479, 3371, 3300, 3055, 2924, 2855, 1623, 1581, 1541, 1472, 1323, 1266, 1253, 1152, 882, 748, 662 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.6 Hz, 3H, CH_3), 1.28−1.33 (m, 10H, 5 × CH_2), 1.57−1.61 (m, 2H, CH_2), 3.36−3.43 (m, 2H, CH_2), 5.49 (s, br, 2H, NH_2), 6.04 (s, br, 1H, NH), 6.62−6.67 (m, 2H, ArH), 7.16−7.22 (m, 1H, ArH), 7.27−7.30 (m, 1H, ArH).

General Procedure for the Synthesis of 2-Aminobenzonitrile (4). $TiCl_4$ (0.5 mL, 5 mmol) was added dropwise using a syringe to a stirred suspension of iron powder (0.56 g, 10 mmol) in freshly distilled anhydrous THF (10 mL) at rt under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to rt, and 8 mL TEA was added. A solution of *o*-nitrobenzamides (1 mmol) in THF (3 mL) was added dropwise. The reaction mixture was then refluxed for about 5 min under N_2. After this period, the TLC analysis of the mixture showed the reaction to be completed. The reaction mixture was quenched with 5% HCl (15 mL) and extracted with $CHCl_3$ (3 × 40 mL). The combined extracts were washed with water (3 × 40 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by recrystallization from 95% ethanol.

2-Amino-4-chlorobenzonitrile (Entry 1, Table 4). White solid (93% yield). mp 158−159 °C (literature value[24] 156−158 °C). IR (KBr) ν: 3456, 3369, 3252, 2213, 1641, 1609, 1565, 1487, 1435, 1266, 1185, 1096, 919, 844, 785 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.51 (s, br, 2H, NH_2), 6.72−6.78 (m, 2H, ArH), 7.32−7.35 (m, 1H, ArH).

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Supporting Information Available. Experimental details, spectroscopic characterization, and X-ray crystallographic data of **2h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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