Full Paper

Applied Organometallic Chemistry

Received: 17 October 2012 Revised: 16 November 2012 Accepted: 30 November 2012 Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI 10.1002/aoc.2956

Copper(I) salt/PEG-400 catalysis in one-pot direct synthesis of 1-aryl-1*H*-indazoles from 2-bromobenzaldehydes and arylhydrazines

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2-Bromobenzaldehydes are condensed and cyclized with arylhydrazines (or their hydrochlorides) in PEG-400 at 110 °C in the presence of a catalytic amount of a copper(I) salt along with a base to give 1-aryl-1*H*-indazoles in high yields. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: 1-aryl-1*H*-indazoles; arylhydrazines; C−N bond formation; copper(I) salts; cyclization; PEG-400

Introduction

It is known that many indazole-containing compounds exhibit a wide spectrum of pharmacological and biological activities such as antidepressant, contraceptive, antitumor, anti-inflammatory, and anti-HIV activities.[1] Thus, besides conventional methods, transition metal-catalyzed synthetic approaches have been attempted because of the facility and efficiency of reaction and the wide availability of substrate. After the discovery of palladium-catalyzed sp^2-carbon–nitrogen bond-forming reaction by the cross-coupling of aryl halides (or triflates) with primary and secondary amines,[2–4] 1-aryl-1*H*-indazoles also could be formed by such a palladium-catalyzed intramolecular amination of arylhydrazones of *o*-halo aromatic carbonyl compounds.[5–10] However, these precedents have some drawbacks requiring cumbersome step-by-step procedure from easily available commercial products, *o*-halo aromatic carbonyl compounds and arylhydrazines (Scheme 1), as well as an expensive consumable palladium catalyst combined with a ligand. To overcome these drawbacks, several groups have disclosed convenient and economical protocols. We reported on the one-pot direct procedure for 1-aryl-1*H*-indazoles from 2-bromobenzaldehydes and arylhydrazines in the presence of a palladium catalyst combined with a phosphorus chelating ligand.[11] It was also disclosed that several copper salts in combination with a ligand can be used to catalyze such an intramolecular amination of arylhydrazones of *o*-halo aromatic carbonyl compounds leading to 1-aryl-1*H*-indazoles.[12–15] Ding *et al.* recently reported on a ligand-free CuI-catalyzed two-step synthesis of 1-aryl-1*H*-indazoles from *o*-halo aromatic carbonyl compounds and arylhydrazines.[16] Under these circumstances, this report describes an efficient ligand-free copper salt-catalyzed one-pot procedure in PEG-400 for the synthesis of 1-aryl-1*H*-indazoles from 2-bromobenzaldehydes and arylhydrazines (or their hydrochlorides).

Results and Discussion

The results of several attempted cyclizations of 2-bromobenzaldehyde (**1a**) with phenylhydrazine (**2a**) for the optimization of reaction conditions are listed in Table 1. Treatment of **1a** with an equimolar amount of **2a** in PEG-400 in the presence of a catalytic amount of CuI (10 mol%) along with NaO^tBu afforded 1-phenyl-1*H*-indazole (**3a**) in 85% isolated yield with complete conversion of **1a**, which was monitored until **1a** had disappeared on thin-layer chromatography (entry 1). In view of the availability of the hydrazine counterpart, it is desirable to use arylhydrazine hydrochloride since most commercially available arylhydrazines are sold as their hydrochloride salts. A similar yield of **3a** was observed with the use of phenylhydrazine hydrochloride in place of phenylhydrazine under the employed conditions (entry 2). Among bases examined under the employment of CuI and PEG-400, Cs_2CO_3 and K_3PO_4 were shown to be as effective as that using NaO^tBu, whereas K_2CO_3 was not effective for the present amination (entries 3–5). Similar catalytic activity to CuI was observed with several copper(I) salts such as CuCl and CuBr in combination with NaO^tBu and PEG-400 (entries 6–8). Here again, phenylhydrazine hydrochloride also could be used in place of phenylhydrazine without any loss of the yield of **3a** under CuI/Cs_2CO_3 and $CuBr/NaO^tBu$ (entries 9 and 10). Among the solvents examined under the employment of CuI and NaO^tBu, PEG-400 in terms of product **3a** yield and complete conversion of **1a** was shown to be the solvent of choice (entries 11–13). This result indicates that PEG-400 plays a pivotal role in the present reaction. It is reported by several groups that poly(ethylene glycol) (PEG) is used as an efficient medium in transition metal-catalyzed reactions.[17–27]

Based on optimized reaction conditions such as $CuI/NaO^tBu/H_2NNHAr$ (condition A), $CuI/NaO^tBu/HCl{\cdot}H_2NNHAr$ (condition B), $CuI/Cs_2CO_3/HCl{\cdot}H_2NNHAr$ (condition C) and $CuBr/NaO^tBu/HCl{\cdot}H_2NNHAr$ (condition D), various 2-bromobenzaldehydes and their analogues were subjected to the reaction with arylhydrazines (or their hydrochloride salts) in order to investigate the reaction scope, and several representative results are summarized in Table 2. 2-Bromobezaldehyde (**1a**) was readily cyclized with an array of

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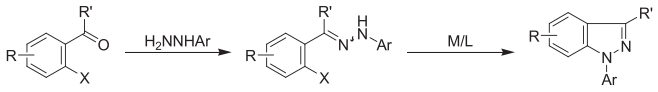
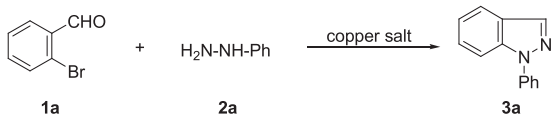


Scheme 1. Synthesis of 1-aryl-1*H*-indazoles.

Table 1. Optimization of conditions for the reaction of **1a** with **2a**[a]



1a **2a** **3a**

Entry	Copper catalyst	Bases	Solvents	Time (h)	Yield (%)
1	CuI	NaO^tBu	PEG-400	2	85
2[b]	CuI	NaO^tBu	PEG-400	2	80
3	CuI	Cs_2CO_3	PEG-400	3	83
4	CuI	K_3PO_4	PEG-400	3	79
5	CuI	K_2CO_3	PEG-400	3	49
6	CuCl	NaO^tBu	PEG-400	5	78
7	CuBr	NaO^tBu	PEG-400	5	83
8	CuOAc	NaO^tBu	PEG-400	5	68
9[b]	CuI	Cs_2CO_3	PEG-400	6	80
10[b]	CuBr	NaO^tBu	PEG-400	6	81
11	CuI	NaO^tBu	DMF	5	47
12	CuI	NaO^tBu	ethylene glycol	5	46
13	CuI	NaO^tBu	toluene	5	0

[a]Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), copper catalyst (0.1 mmol), base (2 mmol), solvent (3 ml), 110 °C.
[b]Phenylhydrazine hydrochloride was used in place of phenylhydrazine.

arylhydrazines (or arylhydrazine hydrochloride salts) (**2a–i**) having electron-donating and -withdrawing substituents on the aromatic ring to give the corresponding 1-aryl-1*H*-indazoles (**3a–i**) in the range of 40–89% isolated yields. Judging from the reaction of **1a** with **2b–d** having electron-donating methyl substituent, the product yield had relevance to the position of the substituent on the aromatic ring of **2b–d**. With *meta*-methyl-substituted **2c**, the product yield was generally higher than that when *para*-methyl-substituted **2b** and *ortho*-methyl-substituted **2d** were used. The reaction with **2d** proceeded invariably under the employed conditions B–D. However, in the reaction with **2f–i** having electron-withdrawing substituents, the product yield was not significantly affected by the position of the substituent. From the reactions between several 2-bromobenzaldehydes **1b–d** and **2a**, the corresponding 1-phenyl-1*H*-indazoles (**3j–l**) were also produced in high yields irrespective of the examined functional groups on the aromatic ring of **1b–d**. Similar treatment of 2-bromonaphthalene-1-carbaldehyde (**1e**)[28,29] under condition D also afforded the cyclized product **3 m**, however, the yield was lower than when 2-bromobenzaldehydes (**1a–d**) were used. 2-Bromopyridine-3-carbaldehyde (**1f**) and 3-bromopyridine-4-carbaldehyde (**1 g**)[30] were also cyclized under the employed condition B to give 1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (**3n**) and 1-phenyl-1*H*-pyrazolo [3,4-*c*]pyridine (**3o**) in 88% and 70% yields, respectively. However, not shown in Table 2, similar treatment of **1a** with methylhydazine did not afford 1-methyl-1*H*-indazole at all. It is difficult to know why arylhydazines are only available for the present system.

Although the details of the reaction scheme are not certain, a plausible pathway is presented in Scheme 2. Oxidative addition of the carbon–bromide bond of hydrazone **4** to a complex **5**, initially formed *in situ* from copper salt and PEG-400, produces an arylcopper complex **6**. This is followed by intramolecular closure to give a complex **7** which can reductively eliminate to afford 1-aryl-1*H*-indazole **3**.

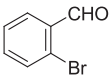
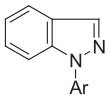
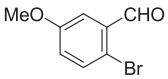
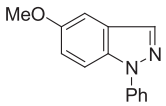
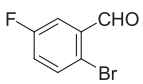
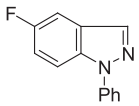
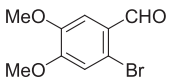
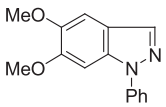
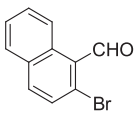
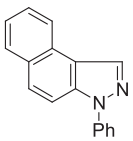
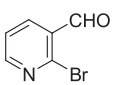
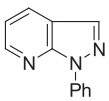
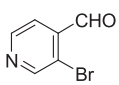
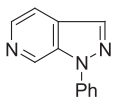
Conclusion

In summary, we have demonstrated that 2-bromobenzaldehydes react with arylhydrazines (or their hydrochlorides) in PEG-400 in the presence of a copper(I) salt along with a base to give 1-aryl-1*H*-indazoles in high yields. The present reaction provides an efficient ligand-free copper(I) salt-catalyzed one-pot procedure for the synthesis of 1-aryl-1*H*-indazoles from 2-bromobenzaldehydes and arylhydrazines. Further study of synthetic applications using a ligand-free catalytic system of copper(I) salts/PEG-400 is in progress.

Experimental

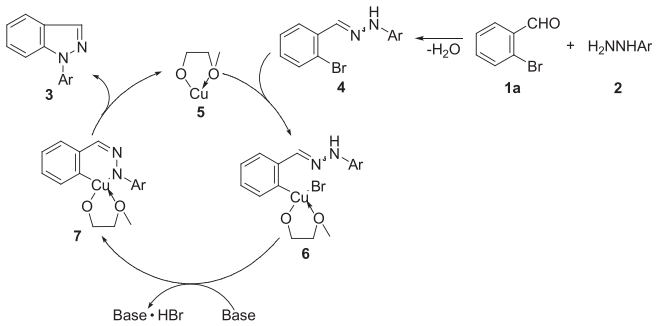
^1H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using tetramethylsilane as an internal standard. Melting points were determined on a Stanford Research Inc. MPA100 automated melting point apparatus. The isolation of pure products was carried out via thin-layer (silica gel 60 GF_{254}, Merck) or column (silica gel 60, 70–230 mesh, Merck) chromatography. 2-Bromonaphthalene-1-carbaldehyde (**1e**) was synthesized in two steps: initial treatment of 2-tetralone

Table 2. CuI-calayzed synthesis of 1-aryl-1*H*-indazoles[a]

1	2	Condition[b]	Time (h)	Product	Yield (%)
	H_2N-NH-Ar or HCl · H_2N-NH-Ar				
1a	**2a** Ar = Ph	A	2	**3a**	85
		B	6		80
		C	6		80
		D	6		81
	2b Ar = 4-MeC_6H_4	B	6	**3b**	63
	2c Ar = 3-MeC_6H_4	B	6	**3c**	89
	2d Ar = 2-MeC_6H_4	B	6	**3d**	40
		C	6		45
		D	5		42
	2e Ar = 4-$MeOC_6H_4$	B	6	**3h**	80
	2f Ar = 4-ClC_6H_4	B	6	**3e**	75
	2g Ar = 3-ClC_6H_4	B	6	**3f**	77
	2h Ar = 2-ClC_6H_4	B	6	**3g**	74
	2i Ar = 2-FC_6H_4	B	6	**3i**	73
					
1b	**2a**	A	6	**3j**	91
		C	6		85
					
1c	**2a**	B	6	**3k**	89
					
1d	**2a**	A	6	**3l**	93
					
1e	**2a**	D	6	**3m**	54
					
1f	**2a**	B	6	**3n**	88
					
1g	**2a**	B	6	**3o**	70

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), copper catalyst (0.1 mmol), base (2 mmol), PEG-400 (3 ml), 110°C.
[b] A: CuI, NaO^{t}Bu, NH_2NHAr; B: CuI, NaO^{t}Bu, HCl · NH_2NHAr; C: CuI, Cs_2CO_3, HCl · NH_2NHAr; D: CuBr, NaO^{t}Bu, HCl · NH_2NHAr.

under bromination conditions of the Vilsmeier–Haack reaction (PBr_3/DMF/$CHCl_3$) to produce 2-bromo-3,4-dihydro-1-naphthaldehyde and aromatization of 2-bromo-3,4-dihydro-1-naphthaldehyde under 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.[28,29] 3-Bromopyridine-4-carbaldehyde (**1 g**) was prepared by the treatment of 3-bromopyridine with lithium diisopropylamide and DMF.[30]



Scheme 2. A catalytic cycle.

Commercially available organic and inorganic compounds were used without further purification.

General Procedure for Copper(I) Salt-Catalyzed Synthesis of 1-Aryl-1*H*-Indazoles from 2-Bromobenzaldehydes and Arylhydrazines (or their Hydrochlorides)

To an organic reactor (Radleys Discovery Technologies) were added 2-bromobenzaldehyde **1** (1 mmol), arylhydrazine (or arylhydrazine hydrochloride) **2** (1 mmol), copper salt (0.05 mmol), base (2 mmol) and solvent (3 ml). The system was stirred at 110 °C for an appropriate time. The reaction mixture was cooled to room temperature, poured into water and extracted with ethyl acetate twice. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by thin-layer (silica gel 60 GF_{254}, Merck) or column (silica gel 60, 70–230 mesh, Merck) chromatography (ethyl acetate–hexane mixture) to give 1-aryl-1*H*-indazoles **2**. Except for **3f**, **3i** and **3 m** (Fig. 1), all products are known.[6,11,16,31,32]

Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.28 (m, 1H, H14), 7.32–7.35 (m, 1H, H7), 7.45–7.49 (m, 2H, H5 and H6), 7.65–7.67 (m, 1H, H4), 7.76–7.83 (m, 3H, H11, H13 and H15), 8.22 (d, J_{HH} = 0.8 Hz, 1H, H3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.51 (C7), 120.60 (C11), 121.72 (C15), 122.11 (C4), 122.89 (C5), 125.74 (C8), 126.76 (C13), 127.76 (C6), 130.66 (C14), 135.35 (C12), 136.26 (C3), 138.81 (C9), 141.47 (C10), assignments to C4 and C5 are interchangeable. Anal. Calcd for $C_{13}H_9ClN_2$: C, 68.28; H, 3.97; N, 12.25. Found: C, 68.25; H, 4.14; N, 12.33.

Solid. m.p. 83–85 °C (hexane–ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.26 (m, 1H, H5), 7.30–7.35 (m, 2H, H13 and H14), 7.39–7.46 (m, 3H, H7, H12 and H15), 7.61–7.65 (m, 1H, H6), 7.80–7.82 (m, 1H, H4), 8.26 (d, J_{HH} = 0.8 Hz, 1H, H3), assignments to H5, H13 and H14 are interchangeable. ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.73 (d, J_{CF} = 5.1 Hz, C15), 117.17 (d, J_{CF} = 19.6 Hz, C12), 121.28 (C7), 121.74 (C4), 124.83 (C8), 125.08 (d, J_{CF} = 3.6 Hz, C14), 127.36 (C5), 127.75 (d, J_{CF} = 11.6 Hz, C10), 128.13 (C6), 129.44 (d, J_{CF} = 8.0 Hz, C13), 136.37 (C3), 140.32 (C9), 156.29 (d, J_{CF} = 251.0 Hz, C11), assignments to C4–C7 are interchangeable. Anal. Calcd for $C_{13}H_9FN_2$: C, 73.57; H, 4.27; N, 13.20. Found: C, 73.58; H, 4.34; N, 13.11.

Solid. m.p. 167–168 °C (hexane–chloroform). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.44 (m, 1H, H17), 7.50–7.54 (m, 1H, H5), 7.56–7.60 (m, 2H, H16), 7.64–7.68 (m, 1H, H6), 7.76–7.78 (m, 4H, H4, H7 and H15), 7.94 (d, J_{HH} = 8.0 Hz, 1H, H9), 8.29 (d, J_{HH} = 8.0 Hz, 1H, H8), 8.62 (s, 1H, H3), assignments to H5, H6 and H17 are interchangeable. ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.42 (C9), 121.04 (C11), 123.21 (C8), 123.64 (C15), 125.06 (C17), 127.44 (C4), 127.53 (C12), 127.75 (C5), 128.87 (C6), 128.91 (C7), 129.74 (C16), 129.82 (C10), 134.31 (C3), 137.33 (C13), 140.17 (C14), assignments to C4–C7 are interchangeable. Anal. Calcd for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47. Found: C, 83.50; H, 4.91; N, 11.45.

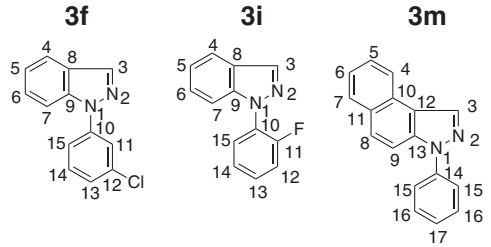


Figure 1. Structures of products **3f**, **3i** and **3 m**.

Acknowledgments

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2012–0002856) and Kyungpook National University Research Fund, 2012.

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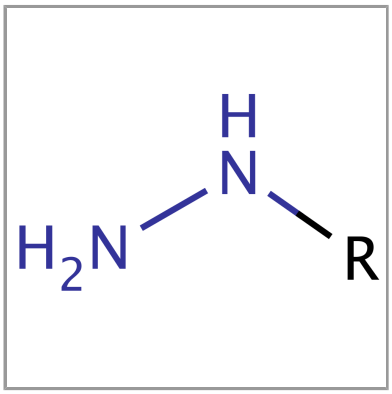

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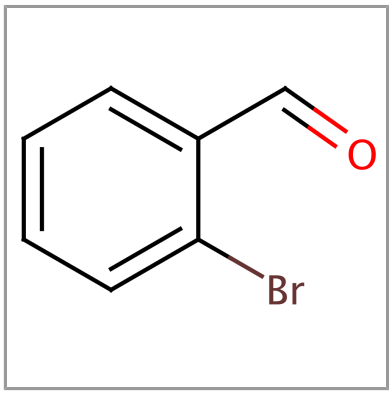

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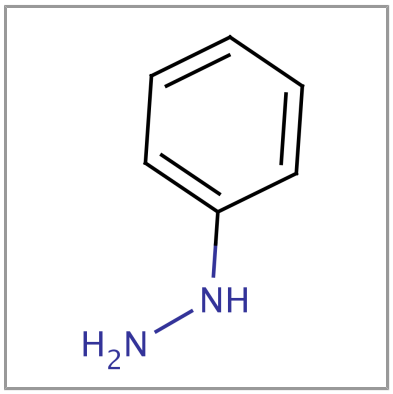

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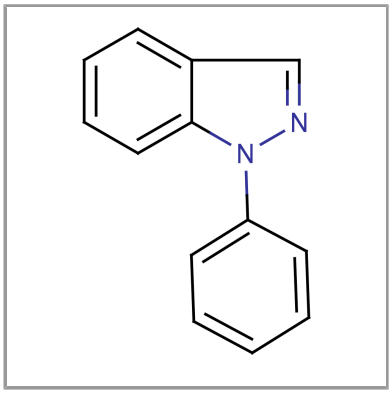

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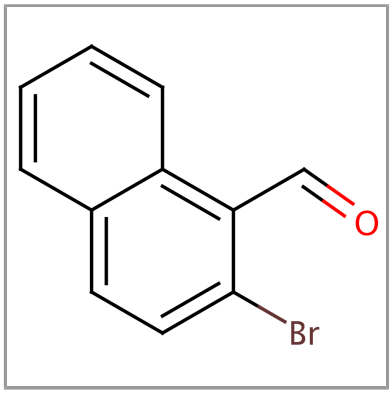

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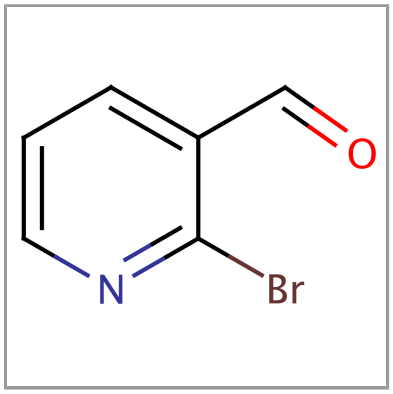

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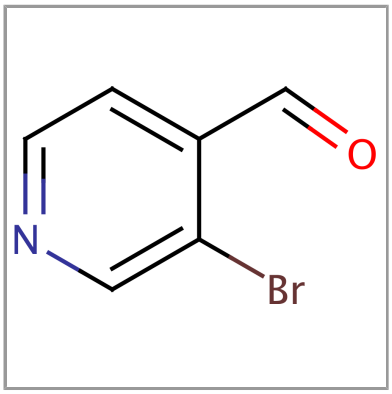

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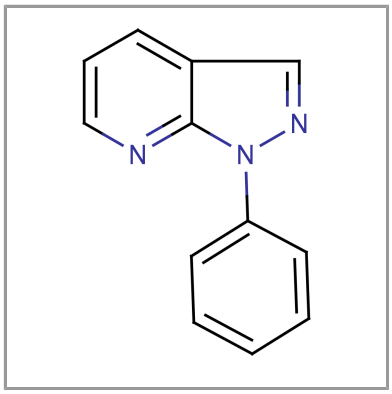

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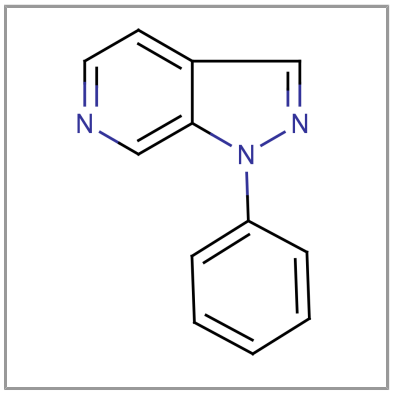

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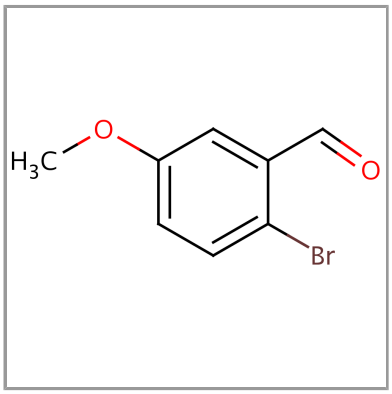

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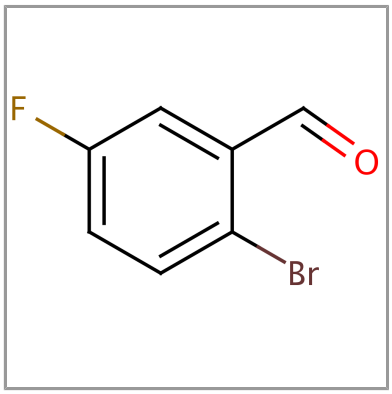

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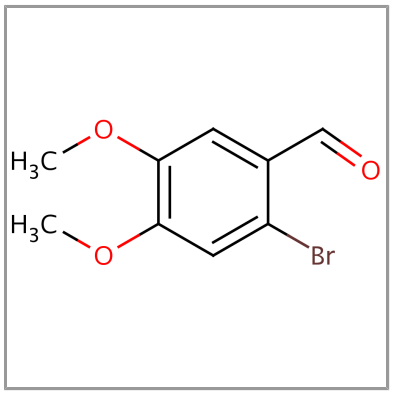

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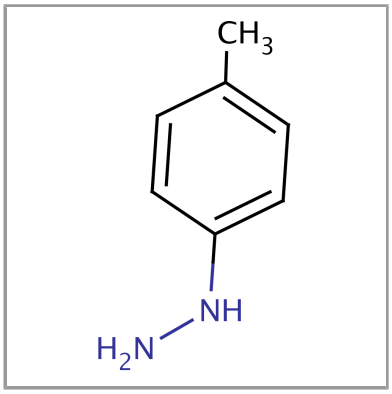

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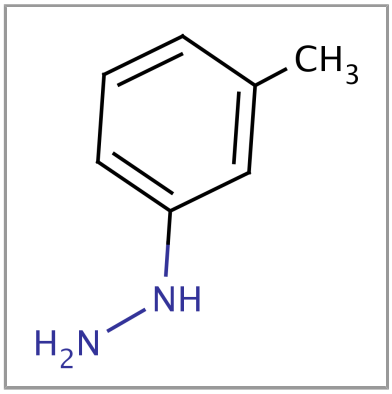

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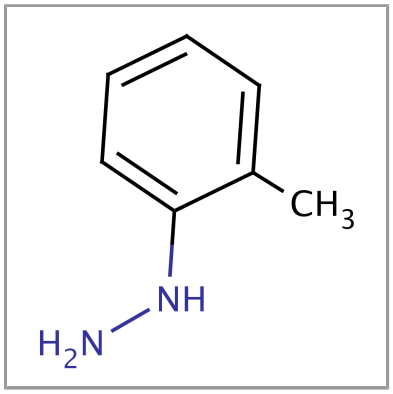

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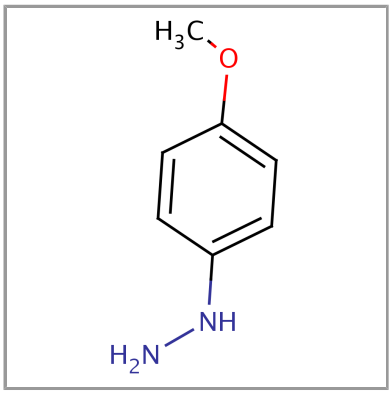

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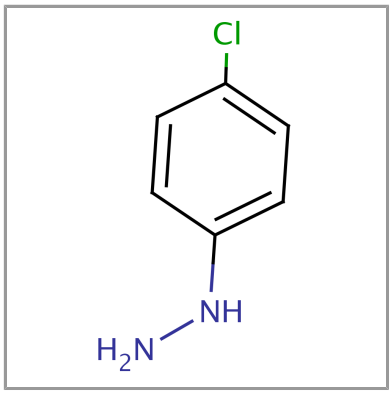

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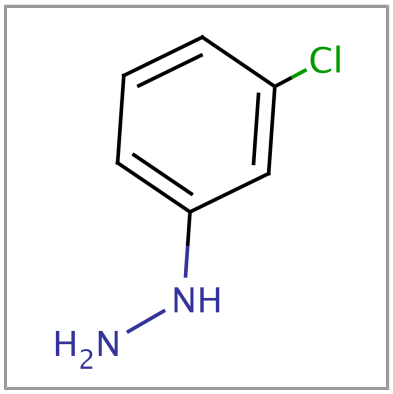

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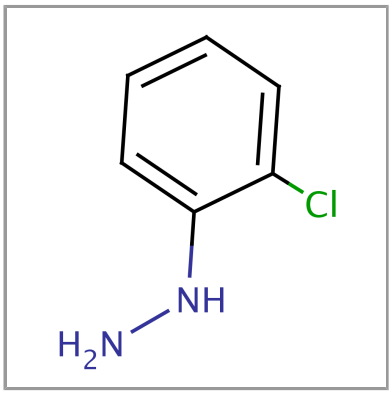

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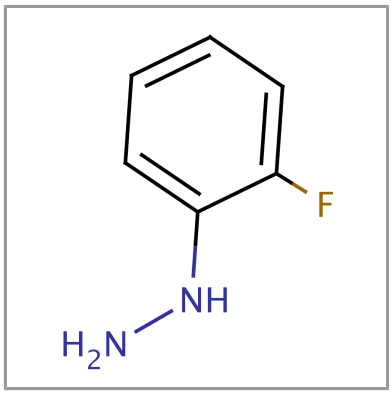

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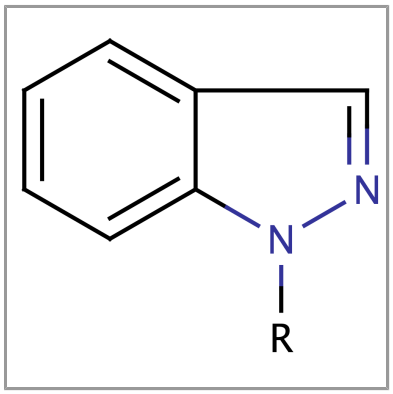

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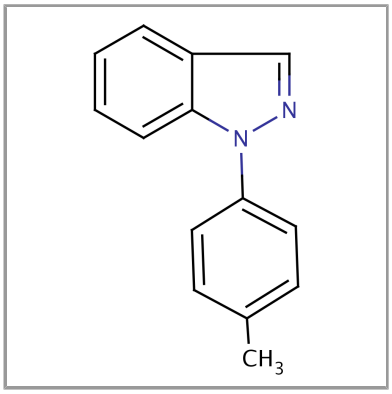

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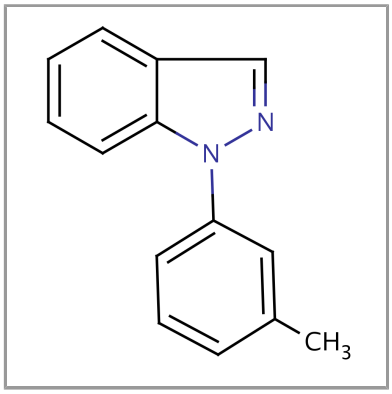

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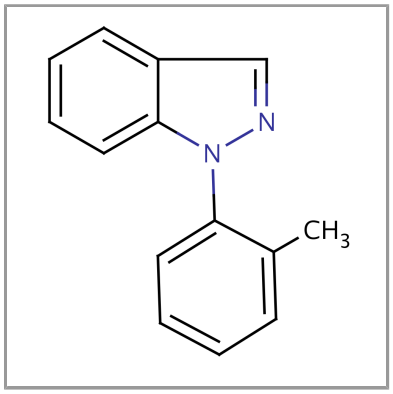

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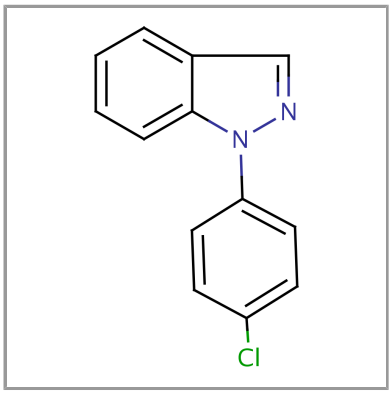

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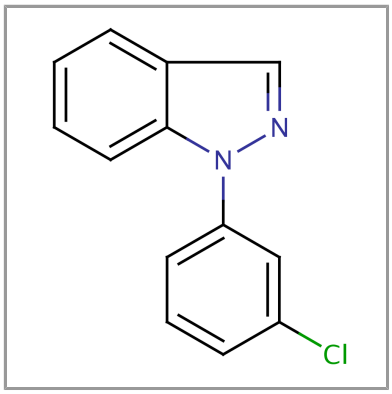

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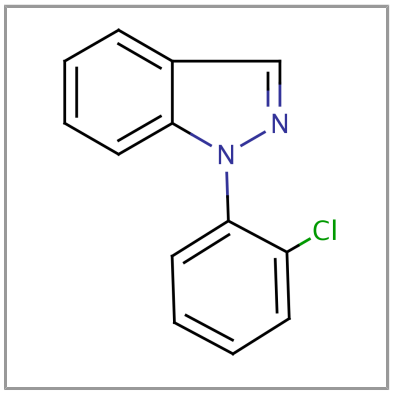

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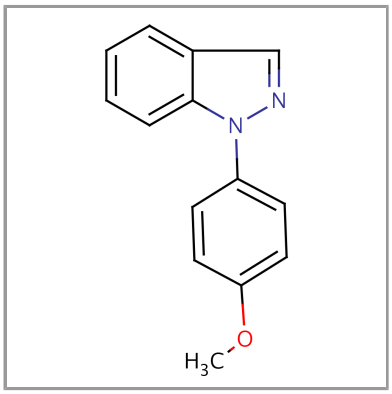

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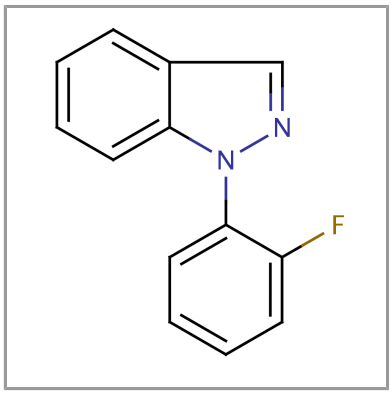

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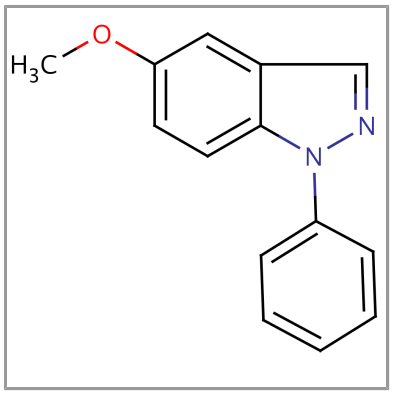

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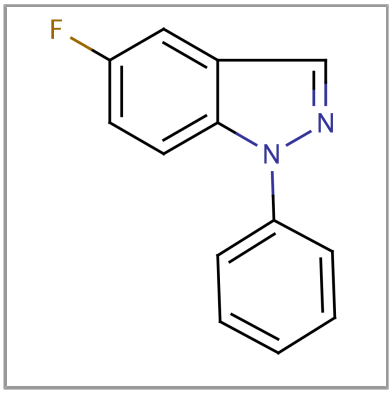

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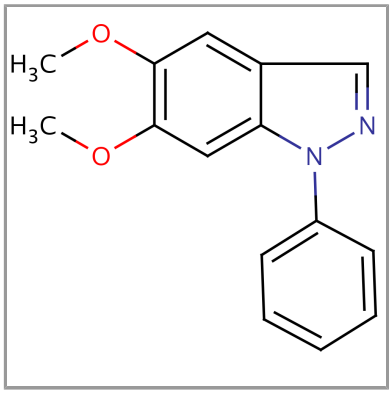

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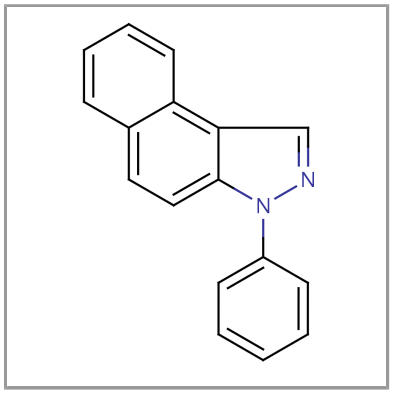

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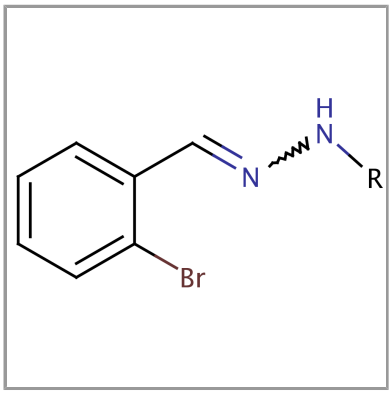

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