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Regioselective Synthesis of 2*H*-Indazoles through Ga/Al- and Al-Mediated Direct Alkylation Reactions of Indazoles

Mei-Huey Lin,* Han-Jun Liu, Wei-Cheng Lin, Chung-Kai Kuo, Tsung-Hsun Chuang

Department of Chemistry, National Changhua University of Education, Changhua, Taiwan 50007

mhlin@cc.ncue.edu.tw

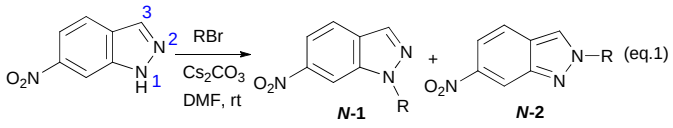
Abstract: A procedure has been developed for the regioselective, high yielding synthesis of 2*H*-indazoles that involves direct alkylation of indazoles with various allyl and benzyl bromides, and α-bromocarbonyl compounds.

Introduction

Numerous medicinal chemical studies have led to the identification of the indazole ring system as a highly effective pharmacophore. This ring system serves as a core component of important nitrogen containing heterocycles that display a broad range of biological properties, such as inhibition of nitric oxide[1] and HIV protease,[2] anti-inflammator,[3] antitumor[4] and anti-cancer[5] activities, and serotonin 5-HT3 receptor antagonist behavior.[6]

Recently, the 2*H*-indazole ring system has been utilized as an important pharmacophore in drug discovery efforts.[7] Compared with their 1*H* analogs, 2*H*-indazoles have been much less studied owing partly to difficulties associated with their preparation. One of the synthetic strategies used to prepare members of the 2*H*-indazole family utilizes the cyclization reaction of properly tethered substrates such as iminonitroaromatics derived from 2-nitrobenzaldehyde and amines, 2-azidoimines derived from 2-azidobenzaldehyde and amine, and [3+2] dipolar

cycloaddition of sydnone and benzyne.[8] Perhaps the most straightforward route to construction of 2*H*-indazoles utilizes direct alkylation reactions of the corresponding 1*H*-indazoles. However, only a very few reactions of this type produce 2*H*-indazoles with high levels regioselectivity.[9] For example, Cheung *et. al*. reported highly regioselective synthesis of 2-methyl and 2-ethyl 2*H*-indazoles from reaction of indazoles with Meerwein's salts under kinetic control conditions.[9] Normally, direct alkylation of indazoles in the presence of a base generally provides a mixture of *N*-1 and *N*-2-alkylation products (eq. 1) or the thermodynamically favored *N*-1 alkylated product predominantly.[10] Therefore, the development of methods to prepare 2*H*-indazoles in a direct and highly regioselective manner through alkylation of indazoles remains a significant challenge in heterocyclic chemistry.



R = allyl; 34% yield of ***N*-1** (***N*-1**:***N*-2** = 1:1)
R = CH_2CO_2Me; 87% yield of ***N*-1** (***N*-1**:***N*-2** = 25:1)

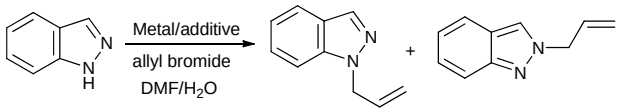
It has been suggested that the *N*-2 lone pair electrons in indazoles participate in kinetically controlled reactions that lead to *N*-protected products (*e. g.,* THP derivatives) when carried out under mildly acidic conditions.[11] Moreover, it has been reported that indazole serves as a chelating ligand for aluminum and gallium cations through coordination utilizing its *N*-2 lone pair.[12] In a related effort, it has been shown that gallium and allyl bromide participate in nucleophilic substitution reactions in aqueous media, as is exemplified by *C*-3 allylation reactions of indoles.[13] These observations led us to propose a new method for regioselective synthesis of 2-substituted 2*H* indazoles that involves gallium-mediated *N*-2 allylation reactions with allyl bromide. We envisaged that an allylgallium/allylaluminium

cation would be generated in this process by reaction of gallium/aluminium metal and allyl bromide and that enables allylation of indazole at the kinetically more reactive *N*-2 position.

Results and discussion

The effort designed to evaluate this proposal began with an investigation of the gallium-mediated allylation reaction between indazole and allyl bromide (Table 1). As anticipated, we observed that the process produces the *N*-2 regioisomer **2a** exclusively with a moderate isolated yield and unreacted indazole starting material (Table 1, entry 1).[14] Screening other metals led to the observation that the use of a combination of gallium and aluminum is optimal for promotion of the alkylation reaction (Table 1, entry 6) and that the efficiency of the process is not increased when a phase transfer reagent such as tetrabutylammonium bromide is present in the reaction mixture (Table 1, entry 8). In addition, when the reaction is performed in the presence of a base such as potassium carbonate (2 equiv, pH of the resulting solution is 10), a mixture of *N*-1 and *N*-2 allylation products is formed (Table 1, entry 9). Finally, adding aqueous hydrobromic acid does not lead to an improvement in the yield of the *N*-2 regioisomer (Table 1, entry 10 *versus* 6).

Table 1. Metal mediated regioselective *N*-2 allylation of indazole[a]



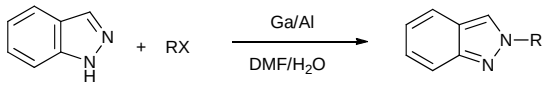
entry	metal/additive (equiv)	**2a'**:**2a**[b]	**2a** (%)[c]
1	Ga (1)	0 : 100	42
2	Ga (2)	0 : 100	44
3	Ga (1)/In (1)	0 : 100	22
4	Ga (1)/Cu (1)	0 : 100	14
5	Ga (1)/Zn (1)	0 : 100	20
6	Ga (1)/Al (1)	0 : 100	54
7	Al (2)	0 : 100	48
8	Ga (1)/Al (1)/Bu_4NBr (1)	0 : 100	33
9	Ga (1)/Al (1)/K_2CO_3 (2)	50 : 50	42
10	Ga (1)/A l(1)/HBr (0.1 mL)	0 : 100	42

[a]Conditions: indazole (1.0 mmol), allyl bromide (2.0 mmol), and indicated metal in DMF (1.5 mL)/water (0.5 mL) at rt. [b]Ratio was determined by ^{1}H NMR. [c]Isolated yield.

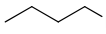
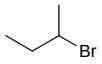
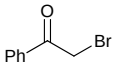
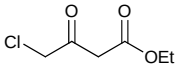
The scope of the Ga/Al-mediated reaction of indazole was explored using a variety of electrophiles (Table 2). The results show that allyl bromide, benzyl bromide and α-bromoacetophenone react with indazole in a highly regioselective and efficient manner (Table 2, entries 1, 4, and 12). In the Ga/Al-mediated reaction of benzyl bromide, benzyl alcohol is also produced. Therefore, an acetylation procedure was employed to chromatographically remove this hydrolysis product and obtain pure 2-substituted 2*H*-indazole **2h**. Importantly, alkyl chlorides (Table 2, entries 2, 5, 13), benzyl acetate (Table 2, entry 6), benzyl trifluoroacetate (Table 2, entry 7) and aliphatic bromides (Table 2, entries 9-11) do not participate in the alkylation reaction. Finally, propargyl bromide and secondary alkyl bromides do serve as substrates but the yields of the processes are low (Table 2, entry 3,

8 *versus* 4).

Table 2. Scope of reaction with various alkylating agents[a]



1 **2**

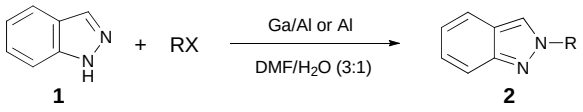
entry	RX	**2**; yield (%)[b]
1	allyl bromide	**2a**; 54 (0:100)[c]
2	allyl chloride	0
3	propargyl bromide	< 5
4	$PhCH_2Br$	**2h**; 70 (0:100)[c]
5	$PhCH_2Cl$	0
6	$PhCH_2OAc$	0
7	$PhCH_2OCOCF_3$	0
8		< 5
9		0
10		0
11		0
12		**2k**; 76 (2:98)[c]
13		0

[a]Conditions: indazole (1.0 mmol), RX (2.0 mmol), Ga (1.0 mmol), and Al (1.0 mmol) in DMF (1.5 mL)/water (0.5 mL) at rt. [b]Isolated yield. [c]*N*-1:*N*-2, ratio was determined by ^{1}H NMR.

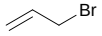
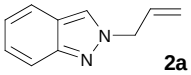
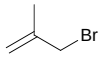
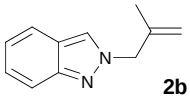
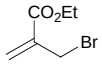
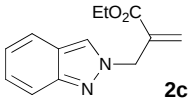
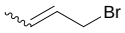
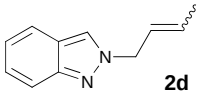
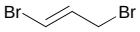
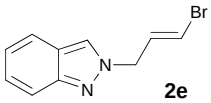
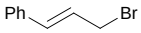
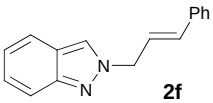
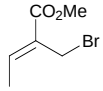
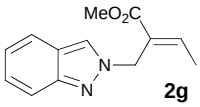
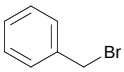
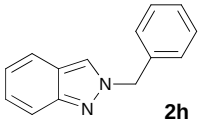
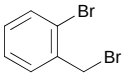
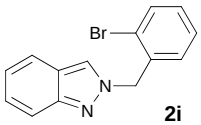
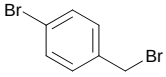
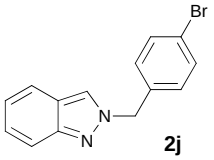
Based on the results summarized in Table 2, reactions of a variety of functionalized allyl and benzyl bromides with indazole were examined (Table 3). The results show that the π-bond stereochemistry of allylic bromides is retained in *N*-2 substituted 2*H*-indazole forming reactions (Table 3, entries 4-7). Moreover, in each case, C-N bond forming reaction occurs at the least substituted carbon of the allylic framework. These observations might suggest the reaction not through π-allyl chemistry, and Lewis acid mediated substitution

reaction could be the scenario. In addition, a variety of α-bromocarbonyl compounds, including arylacyl bromides, 1-bromopinacolone and ethyl bromoacetate, also participate in this process (Table 4, entries 7 and 8). Due to poor solubility of some arylacyl bromides in Ga/Al-mediated reaction condition at ambient temperature; therefore, heating was employed to solve the solubility problem (Table 4, entries 2-6). As can be seen in Tables 3 and 4, yields of the *N*-2 alkylation can be dramatically improved at higher reaction temperature and in more concentrated reaction solution (yields are shown in parentheses). The advantage of using a combination of gallium and aluminum over aluminum seems not obviously necessary at ambient temperature (Table 1, entry 6 versus 7). Therefore, Al-mediated reaction of indazole was also explored using a variety of electrophiles (Table 3 and 4) and Al-mediated reaction is applicable to indazoles, which possess a variety of aryl ring substituents (Table 5). However, when the nucleophilicity of indazole is reduced by the presence of the strong electron-withdrawing substituents (*e. g.,* nitro) yields of the processes are lower (Table 5, entries 1 and 2). Finally, the allylation reaction takes place in the normal fashion even in the case of an indazole substrate bearing an amino substituent (Table 5, entry 4).

Table 3. Scope of allylation and benzylation reactions

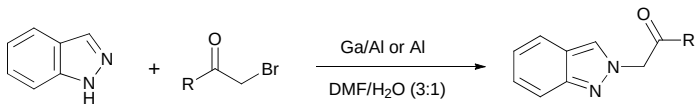


1 **2**

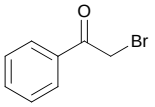
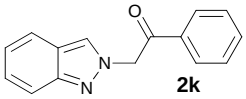
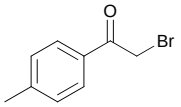
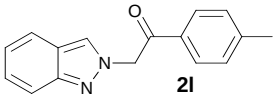
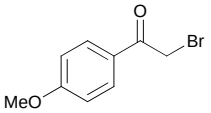
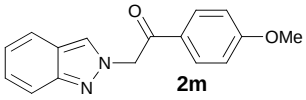
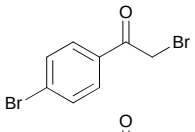
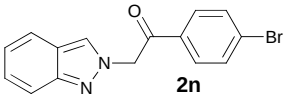
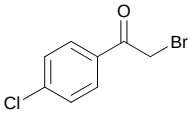
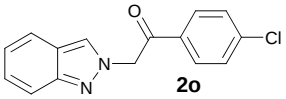
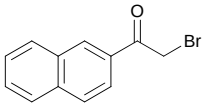
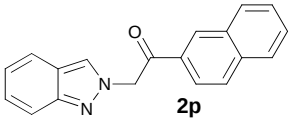
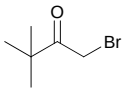
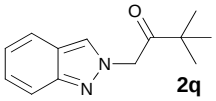
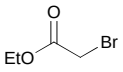
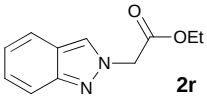
entry	RX	product	**2**; yield[a] (%) from Ga/Al	**2**; yield[a] (%) from Al
1		 **2a**	54 (88)[b]	48 (87)[b]
2		 **2b**	45 (84)[b]	
3		 **2c**	82	92
4[c]		 **2d**	54 (71)[c]	(68)[c]
5		 **2e**	49 (90)[b]	
6		 **2f**	50 (69)[b]	(68)[b]
7		 **2g**	58 (83)[b]	
8		 **2h**	70 (81)[d]	(91)[d]
9		 **2i**	66 (90)[d]	
10		 **2j**	64 (76)[d]	

[a]Conditions: indazole (1.0 mmol), RX (2.0 mmol), Ga/Al (1.0 mmol, each) or Al (2.0 mmol) in DMF/H_2O (2.0 mL) at rt. [b]Conditions: indazole (1.0 mmol), RX (3.0 mmol), Ga/Al (1.5 mmol, each) or Al (3.0 mmol) in DMF/H_2O (1.0 mL) at 55 ^oC. [c]Conditions: indazole (1.0 mmol), crotyl bromide (85%, 4.0 mmol), Ga/Al (1.5 mmol, each) or Al (3.0 mmol) in DMF/H_2O (1.0 mL) at 55 ^oC. [d]Conditions: indazole (1.0 mmol), RX (2.0 mmol) Ga/Al (1.0 mmol, each) or Al (2.0 mmol) in DMF/H_2O (1.0 mL) at 55 ^oC.

Table 4. Scope of α-bromocarbonyl compounds

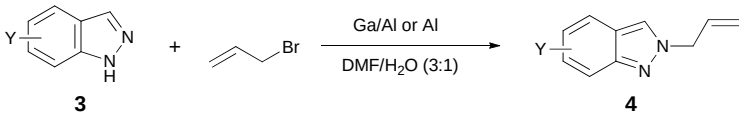


1 **2**

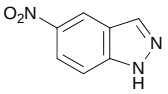
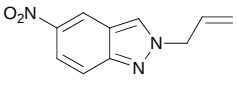
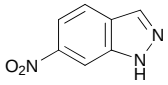
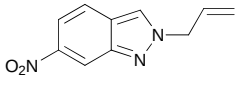
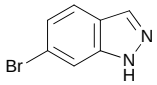
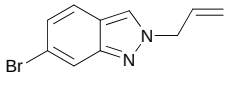
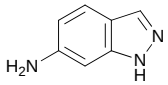
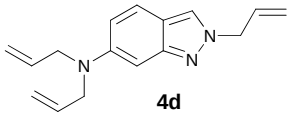
entry	$RCOCH_2Br$	product	**2**; yield[a] (%) from Ga/Al	**2**; yield[a] (%) from Al
1		 **2k**	76[b]	97[b]
2		 **2l**	78	75
3		 **2m**	79	--
4		 **2n**	78	--
5		 **2o**	74	73
6		 **2p**	82	--
7		 **2q**	70[b] (94)[c]	(89)[c]
8		 **2r**	74[b] (82)[c]	--

[a]Conditions: indazole (1.0 mmol), $ArCOCH_2Br$ (2.0 mmol), Ga/Al (1.0 mmol, each) or Al (2.0 mmol) in DMF/H_2O (2.0 mL) at 55 °C. [b]Conditions: indazole (1.0 mmol), $PhCOCH_2Br$ (2.0 mmol), Ga/Al (1.0 mmol, each) or Al (2.0 mmol) in DMF/H_2O (2.0 mL) at rt. [c]Conditions: indazole (1.0 mmol), $RCOCH_2Br$ (3.0 mmol), Ga/Al (1.5 mmol, each) and Al (3.0 mmol) in DMF/H_2O (1.0 mL) at 55 °C.

Table 5. Scope of indazoles



3 **4**

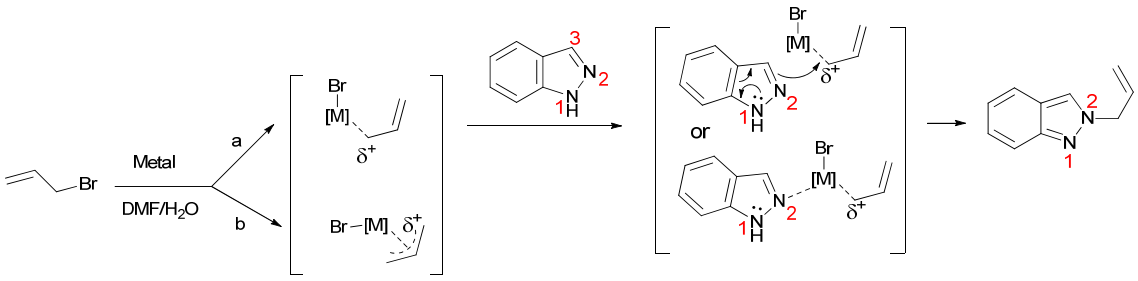
entry	substrate	product	**4**, yield (%)[a] from Ga/Al	**4**, yield (%)[a] from Al
1	 **3a**	 **4a**	55	32
2	 **3b**	 **4b**	50	38
3	 **3c**	 **4c**	78	74
4[b]	 **3d**	 **4d**	80	--

[a]Conditions: indazole (1.0 mmol), allyl bromide (3.0 mmol), Ga/Al (1.5 mmol, each) or Al (3.0 mmol) in DMF (0.75 mL)/water (0.25 mL) at 55 °C. [b]Conditions: indazole (1.0 mmol), allyl bromide (6.0 mmol), Ga/Al (3.0 mmol, each) in DMF/H_2O (1.0 mL) at 55 °C.

A plausible mechanism is proposed in Scheme 1 (taking allyl bromide as an example). Reaction of gallium (aluminium) metal and allyl bromide generates an allylgallium (allylaluminium) cation complex. Highly regioselective synthesis of 2-alkyl 2*H*-indazoles via reaction of indazole with a carbocation intermediate has been reported. [9,11] Generation of the allylic cation would give two possible pathways (a: η1-allyl complex, b: η3 π-allyl cation). Results of Table 3 show that the π-bond stereochemistry of allylic bromides is retained in *N*-2 substituted 2*H*-indazole forming reactions (Table 3, entries 4-7). Moreover, in each case, C-N bond forming reaction occurs at the least substituted carbon of the allylic framework. These observations might suggest the reaction not through π-allyl chemistry. Meanwhile, it has been reported that indazole serves as a chelating ligand for aluminum and gallium cations through coordination utilizing its N-2 lone pair.[12] Therefore, reaction of indazole with η1-allyl

complex could go through chelation or non-chelation pathway, which enables the kinetically controlled reaction that leads to 2-allyl-2*H*-indazole.

Scheme 1. Plausible mechanism.



Conclusions

In the studies described above, we have developed a simple and efficient method for the regioselective synthesis of 2-substituted alkyl 2*H*-indazole that utilizes Ga/Al- and Al-mediated reactions of allyl and benzyl and α-bromo-carbonyl compounds with indazoles. This method has been found to be generally useful for the preparation of a wide variety of 2-alkyl 2*H*-indazoles and some of which are difficult to make in such high overall yields via the conventionally reported approaches.

Acknowledgment

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14. Regiochemistry of the product **2a** was determined by observing a correlation between the proton at C3 of indazole and the carbon at the allylic position from the HMBC NMR spectroscopic experiment.