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Selective Synthesis of 1-Functionalized-alkyl-1*H*-indazoles[§]

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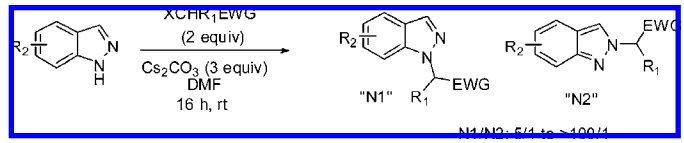
ABSTRACT



An efficient method for the selective "N1" alkylation of indazoles is described. Use of α-halo esters, lactones, ketones, amides, and bromoacetonitrile provides good to excellent yield of the desired N1 products.

The indazole ring is a commonly utilized template in the discovery of pharmacologically active compounds. The ability to manipulate the substitution pattern is therefore crucial to successful drug research. Classically used as a mimic for the more electron-rich indole moiety, the indazole has come into fashion as an effective hinge binding motif in the kinase inhibitor literature.[1] In terms of substitution reactions, the indazole ring (Figure 1) possesses two nitrogens capable of reacting with electrophiles. In the absence of base, the N2 product is often the major, if not exclusive, product.[2] The addition of aqueous base, heating the reaction, and altering the nature of the electrophile are all published strategies to provide a greater proportion of the N1 product.[3] However, the selective alkylation of the N1 position remains a challenge, specifically for C3-unsubstituted indazoles.[4] Presented herein is a method for selective N1 alkylation of

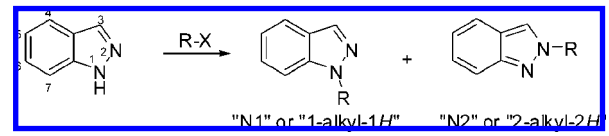


Figure 1. Indazole ring system and alkylation products.

indazoles[5] utilizing α-halo esters, ketones, lactones, amides, and bromoacetonitrile.

The initial alkylations of commercially available 6-nitroindazole with common bromides provided an expected mixture of N1 and N2 alkylation products (Table 1, entries 1−3). However, the use of methyl bromoacetate furnished the N1 product in good yield and excellent selectivity (entry 4). A review of the literature offered no explanation for this result despite a previous report of the alkylation of 6-nitroindazole with ethyl bromoacetate.[6] Since the addition of an electron-withdrawing ester provided high N1 selectivity,

[§] Dedicated to Professor Paul A. Grieco on the occasion of his 65th birthday.

(1) A SciFinder search of the indazole core structure returned 57,227 individual hits. A text search of indazole returned 4,364 references.

(2) Cheung, M.; Boloor, A.; Stafford, J. A. *J. Org. Chem.* **2003**, *68*, 4093.

(3) (a) Von Auwers, K.; Allardt, H.-G. *Ber.* **1924**, *57B*, 1098. (b) Jaffari, G. A.; Nunn, A. J. *J. Chem. Soc. Perkin Trans. 1* **1973**, 2371. (c) Morel, S.; Boyer, G.; Coullet, F.; Galy, J.-P. *Synth. Commun.* **1996**, *26*, 2443. (d) Boyer, G.; Galy, J.-P.; Barbe, J. *Heterocycles* **1995**, *41*, 487.

(4) For a selective N1 substitution via a reversible 1,4 addition, see: Saenz, J.; Mitchell, M.; Bahmanyar, S.; Stankovic, N.; Perry, M.; Craig-Woods, B.; Kline, B.; Yu, S.; Albizati, K. *Org. Process Res. Dev.* **2007**, *11*, 30–38.

(5) For brevity, we refer to the "1-alkyl-1*H*" and "2-alkyl-2*H*" products as the "N1" and "N2" products, respectively.

(6) (a) The high yield of the isolated product implies good selectivity: Muri, E. M. F.; Mishra, H.; Avery, M. A.; Williamson, J. S. *Synth. Commun.* **2003**, *33*, 1977. (b) The reaction of methyl bromoacetate with 6-nitroindazole was reported in 34% yield: Han, Q.; Dominguez, C.; Stouten, P. F. W.; Park, J. M.; Duffy, D. E.; Galemmo, R. A., Jr.; Rossi, K. A.; Alexander, R. S.; Smallwood, A. M.; Wong, P. C.; Wright, M. M.; Leuttgen, J. M.; Knabb, R. M.; Wexler, R. R. *J. Med. Chem.* **2000**, *43*, 4398.

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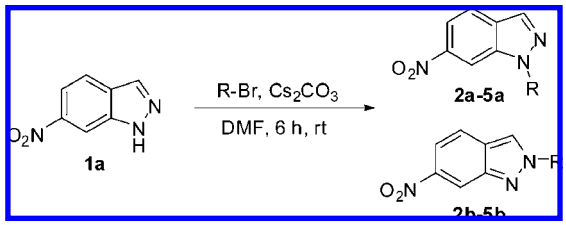
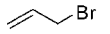
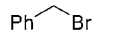
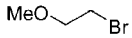
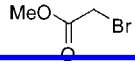
Table 1. Electron-Withdrawing Group Improves N1 Selectivity[a]



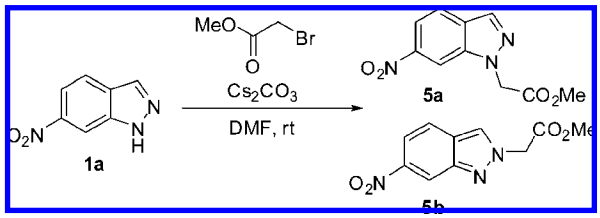
entry	R-Br	a:b ratio	yield
1		1:1	34% of **2a**
2		1.2:1	53% of **3a**
3		1.3:1	58% of **4a**
4		25:1	87% of **5a**

[a] Reaction conditions: 0.3 M, 2 equiv R-Br, 3 equiv Cs_2CO_3.

whereas the inductively withdrawing methoxy group did not (entry 3), a series of variables were investigated to determine the source of selectivity.

First, the reaction of 6-nitroindazole with methyl bromoacetate was followed by HPLC to determine overall conversion of starting material and N1 versus N2 selectivity. Remarkably, the selectivity for alkylation of 6-nitroindazole with methyl bromoacetate greatly increased over time. Table 2 shows that 6-nitroindazole is converted to a mixture of

Table 2. Selectivity versus Time[a]



entry	time (h)	**5a**:**5b** ratio	conversion (%)
1	0.5	3:1	90
2	3	9:1	98
3	6	25:1	99
4	16	131:1	100
5	48	135:1	100

[a] Reaction conditions: 0.3 M, 2 equiv R-Br, 3 equiv Cs_2CO_3.

N1 and N2 products rapidly at rt. However, the N1:N2 ratio gradually increased from 3:1 at 0.5 h to >130:1 at 16 and 48 h without substantial change in yield. Given the similarity of the 16 and 48 h time points, all further experiments were evaluated at 16 h. In reactions of 6-nitroindazole with allyl bromide, benzyl bromide, or 1-bromo-2-methoxyethane, no increase of the N1:N2 ratio was seen with prolonged reaction times.

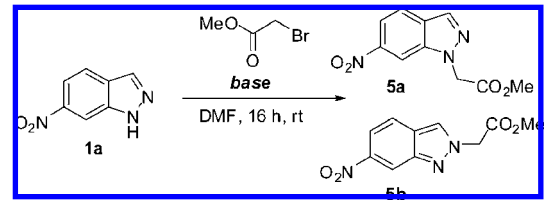
If 6-nitroindazole is treated with 1 equiv each of methyl bromoacetate and cesium carbonate, the ratio of N1:N2 is 3:1 after 1 h and remains unchanged after 16 h. However, treatment with an additional 0.5 equiv of methyl bromoacetate and cesium carbonate rescues the selectivity, providing >130:1 ratio of the N1:N2 products after 2 h. These results suggest thermodynamic control for the alkylation with methyl bromoacetate, in contrast to the other electrophiles that lead to kinetic product distribution.

The effect of the leaving group was next examined. Employing the commercially available ethyl esters of chloro-, bromo-, and iodoacetate, the leaving group showed minimal effect. All three reagents worked effectively, providing good to excellent N1 selectivity. Although ethyl and methyl bromoacetate are employed in most of this work, ethyl chloroacetate works equally well, is a more potent reagent (mol/g), and is a weaker lachrymator.

Seeing little effect of the halide leaving group, a series of common solvents were screened for the conversion of **1a** to **5a**. DMF, DMA, acetone, and THF provided the best conversion (75−100%), N1 selectivity (63:1 to >100:1), and yield (78−85%). In contrast, dichloromethane, *p*-dioxane,[7] and toluene as solvent resulted in poor N1 selectivity (<3:1). Overall, DMF provided the best results across a range of electrophiles and indazoles.

Having found DMF as an optimal solvent, the importance of the base was explored (Table 3). Good to moderate

Table 3. Effect of Base on Conversion and Selectivity[a]



entry	base	conversion (%)	a:b ratio	yield of **5a** (%)
1	Cs_2CO_3	100	131:1	87
2	K_2CO_3	100	92:1	80
3	DIEA	100	2.2:1	ND
4	DBU	81	9:1	ND
5	proton sponge	68	19:1	44
6	NaH	99	1.9:1	ND
7	CsOH	77	63:1	61

[a] Reaction conditions: 0.3 M, 2 equiv R-Br, 3 equiv base.

selectivity was observed with cesium carbonate, potassium carbonate, cesium hydroxide, DBU, and proton sponge.[8] The wide range in N1 selectivity from <2:1 (sodium hydride) to 131:1 (cesium carbonate) was unexpected. In addition to the importance of base for N1 selectivity and overall yield, a few other observations deserve comment. First, the concen-

(7) The poor selectivity with dioxane (~1:1) allowed for isolation of the pure N2 product for mechanistic studies.

(8) Proton sponge: 1,8-bis(dimethylamino)naphthalene.

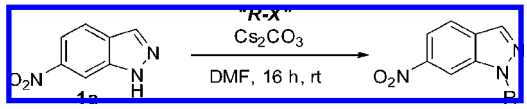
tration of the reaction mixture had a measurable effect on some of the less selective bases (all reactions herein were 0.3 M relative to the indazole). For example, the N1 selectivity with sodium hydride varied nonreproducibly from ~1:1 to as high as 8:1 with slight variations in concentration (0.1 to 0.4 M). Second, the particle size and grade of the carbonate bases proved important for reproducibility across different reaction scales (10 mg to multikilogram). Dry, fine mesh cesium or potassium carbonate reliably provided N1 products selectively and in good to excellent yield, whereas granulated forms were less reproducible. Decreasing the equivalents of base from 3 to 2 was tolerated in many cases, as was lowering the halo acetate equivalents to 1.5. The effect of decreasing the reagent equivalents was empirically determined (often necessary for large-scale reactions and multifunctional indazoles) and studied on a case by case basis, but the higher reagent loading consistently provided good yields and selectivity. Finally, pouring the reaction mixtures directly into a rapidly stirred solution of 2% acetic acid in water often yielded a workable solid, eliminating a traditional workup and/or column purification.

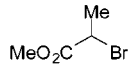
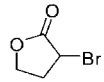
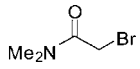
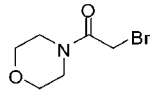
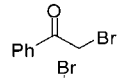
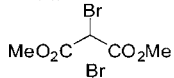
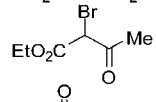
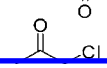
To expand the synthetic utility of this reaction, other electron-withdrawing groups were examined (Table 4). No appreciable loss in selectivity is observed with simple changes at the alcohol portion of the ester (entries 1−3). Substitution in the α position is tolerated, although with loss in selectivity (entries 4 and 5). The α-bromo amides (entries 6 and 7) and bromoacetonitrile serve as selective electrophiles providing moderate yields of the N1 product. Chloroacetone is an extremely selective and effective electrophile, providing 95% of the isolated N1 product (entry 12). Bromoacetophenone and methyl bromoacetoacetate (entries 9 and 11) were selective electrophiles, although product purification proved difficult as a result of side reactions (aldol reactions, multiple alkylation, etc.).[9] Reducing the loading of base and electrophile did not, unfortunately, allow for clean isolation of the desired products. In general, products containing readily enolizable ketones were difficult to purify (substitution of the aryl group did not improve the purification difficulties). In contrast, the product of bromomalonate was readily isolated, providing moderate selectivity and yield of the desired product (entry 10).

The final factors investigated were the substitution and electron density effects of the indazole substrates (Table 5). The 6- and 5-nitrated indazoles provide a similar high yield of selectivity, in sharp contrast to 7-nitroindazole[10] (entries 1−3). The *peri*-interaction between the 7-nitro and the N1 substituent is the likely factor disfavoring the N1 selectivity. The more electron-rich 5-methoxy and unsubstituted indazoles (entries 4 and 5) provide the corresponding N1 products in good yield with high selectivity. The Boc protected indazole anilines (entries 6 and 7) alkylated with modest selectivity at the N1 position only if the number of equivalents of cesium carbonate was lowered to 1.1 (use of 3 equiv led to N-alkylation of the carbamate). The brominated indazole and the 5-ethoxycarbonylindazole were moderately selective for N1, still providing a good yield of the isolated N1 products. Finally, introducing a C-3 substituent predictably increases the N1 selectivity (>200:1, entry 11).

The observed equilibration between the N1 and N2 products is precedented by acylated indazoles,[11] indazole nucleosides,[12] and *N*-pyridinium indazoles.[13] Further, the equilibration of the N2 to N1 product is consistent with greater calculated (>4.1 kCal/mol)[14] and measured[15] stability of 1*H*-indazole versus 2*H*-indazole. Since the N2 product equilibration is unique to the α-electron-withdrawing group halides (see Table 1), the mechanism was not immediately obvious.

Table 4. α-Halo Ester, Amide, Nitrile, and Ketone Electrophiles[a]



entry	R-X	*N1:N2* ratio	yield of **N1**
1	MeO_2CCH_2Br	131:1	87%
2	EtO_2CCH_2Br	125:1	84%
3	*t*-BuO_2CCH_2Br	103:1	69%
4		5.7:1	60%
5		5.6:1	82%
6		25:1	51%
7		27:1	54%
8		27:1	65%
9		>25:1	N.D.
10		6.5:1	67%
11		4.3:1	N.D.
12		100:1	95%

[a] Reaction conditions: 0.3 M, 2 equiv R-X, 3 equiv Cs_2CO_3.

(9) Under solvent-free conditions, microwave radiation cleanly provides the N1 product of indazole and 2-bromo-1-(4-bromophenyl)ethanone: Pérez, E.; Sotelo, E.; Loupy, A.; Mocelo, R.; Suarez, M.; Pérez, R.; Autié, M. *Heterocycles* **1996**, *43*, 539.

(10) Atwell, G. J.; Sykes, B. M.; O'Conner, C. J.; Denny, W. A. *J. Med. Chem.* **1994**, *37*, 371.

(11) (a) Von Auwers, K.; Ernecke, A.; Wolter, E. *Ann.* **1930**, *478*, 154. (b) Yamazaki, T.; Baum, G.; Shechter, H. *Tetrahedron Lett.* **1974**, *15*, 4421.

(12) Boryski, J. *Pol. J. Chem.* **1999**, *73*, 1019.

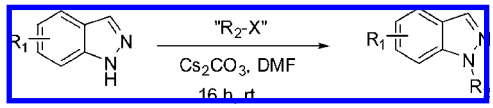
(13) Isin, E. M.; de Jonge, M.; Castagnoli, N., Jr. *J. Org. Chem.* **2001**, *66*, 4220.

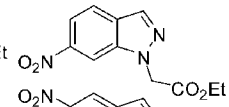
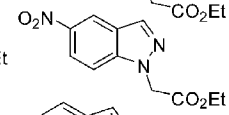
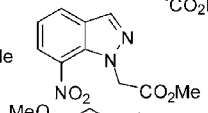
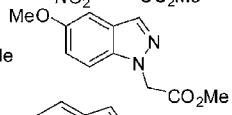
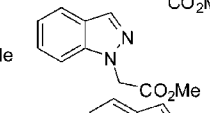
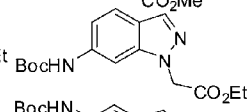
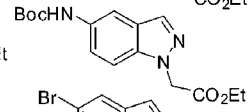
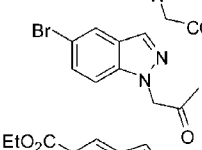
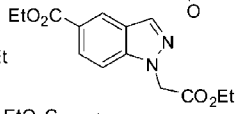
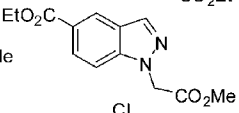
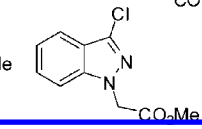
(14) Catalan, J.; de Paz, J. L. G.; Elguero, J. *J. Chem. Soc. Perkin Trans. 2* **1996**, 57.

(15) Elguero, J. *J. Phys. Chem.* **1994**, *98*, 10606.

(16) See Supporting Information.

Table 5. Indazole Variation[a]



entry	R_2-X	product	*N1*:*N2*	yield of *N1*
1	$BrCH_2CO_2Et$		125:1	84%
2	$BrCH_2CO_2Et$		63:1	77%
3	$BrCH_2CO_2Me$		1:1	ND
4	$BrCH_2CO_2Me$		23:1	75%
5	$BrCH_2CO_2Me$		57:1	70%
6[b]	$BrCH_2CO_2Et$		10:1	77%
7[b]	$BrCH_2CO_2Et$		5:1	68%
8	$ClCH_2COMe$		7.2:1	65%
9	$BrCH_2CO_2Et$		6:1	83%
10	$BrCH_2CO_2Me$		13:1	65%
11	$BrCH_2CO_2Me$		>200:1	64%

[a] Reaction conditions: 0.3 M, 2 equiv R_2-X, 3 equiv Cs_2CO_3. [b] Reaction conditions for entries 6 and 7: 0.3 M, 2 equiv R_2-X, 1.1 equiv Cs_2CO_3.

The necessity of excess alkylating reagent (or the addition of the likely byproduct diethyl fumarate)[16] for greater selectivity points to the formation of a β-indazole succinate capable of elimination to the unalkylated indazole starting material (Figure 2). This β-elimination step is similar to the

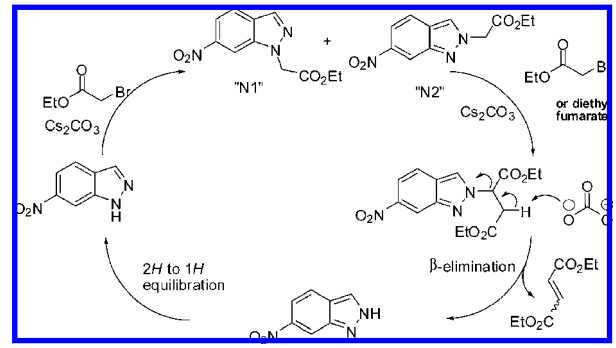


Figure 2. C-Alkylation of N2 ester.

mechanism invoked for the equilibration of N2 to N1 indazole 1,4-addition products in the reaction of an advanced indazole intermediate with ethyl acrylate or ethyl 3-bromopropanoate.[4]

In summary, we disclose a convenient, reliable method for the selective N1 alkylation of indazoles with appropriate electrophiles. α-Halo esters, lactones, ketones, amides, and bromoacetonitrile provide good to excellent yields of the desired N1 products. The reaction proceeds equally well with both electron-rich and -deficient indazoles, except in the case when a C7−N1 *peri*-interaction is introduced. The unique N1 selectivity of this reaction is likely due to the N2 to N1 equilibration via a β-indazole succinate (or equivalent in the amide, nitrile, and ketone examples).

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Supporting Information Available: General synthetic procedure, mechanism support, ^{1}H NMR of N1 products, nuclear Overhouser enhancement correlation, and total correlation spectroscopy (TOCSY) experiment. This material is available free of charge via the Internet at http://pubs.acs.org.

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