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New Practical Synthesis of Indazoles via Condensation of *o*-Fluorobenzaldehydes and Their *O*-Methyloximes with Hydrazine

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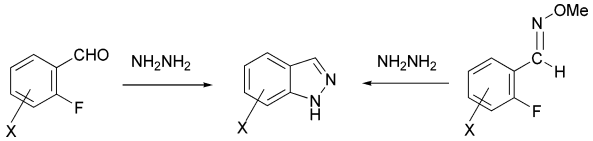
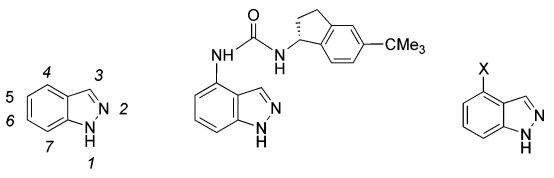


The reaction of *o*-fluorobenzaldehydes and their *O*-methyloximes with hydrazine has been developed as a new practical synthesis of indazoles. Utilization of the methyloxime derivatives of benzaldehydes (in the form of the major *E*-isomers) in this condensation effectively eliminated a competitive Wolf−Kishner reduction to fluorotoluenes, which was observed in the direct preparations of indazoles from aldehydes. Reaction of *Z*-isomers of methyloximes with hydrazine resulted in the formation of 3-aminoindazoles via a benzonitrile intermediate.

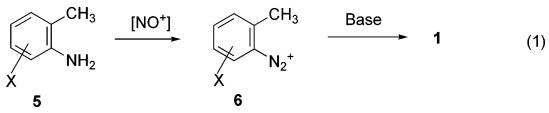
Introduction

Investigation of biologically active compounds possessing the indazole (**1**) heterocyclic core has resulted in the discovery of potent HIV protease inhibitors, serotonin receptor antagonists, aldol reductase inhibitors, and acetylcholinesterase inhibitors.[1,2] Recently, another indazole derivative, ABT-102 (**2**), has been identified as a potent vanilloid receptor (VR1) antagonist. Compound **2** is currently undergoing advanced clinical development for the treatment of chronic pain.[3]



1 **2**, ABT-102 **3**, X = Br **4**, X = Cl

The current synthesis of **2** utilizes 4-haloindazoles **3** or **4** as starting materials. Development of a reliable and efficient preparation of these indazoles was required to provide access to large quantities of bulk drug for the studies. Inspection of the literature[4] revealed that the indazoles substituted on the six-membered ring (including **3** and **4**) were generally prepared via diazotation of the corresponding toluidines **5** (eq 1)[5,6] or the



5 **6** (1)

nitrozation of their *N*-acetyl derivatives **7** (Jacobsen modification, eq 2).[7,8]

Unfortunately, these methods could not be considered practical for multikilogram preparations.[9,10]

Other innovative approaches for indazoles synthesis have been reported, but they either gave mixtures of isomeric products[11] or were only limited to the synthesis of indazoles substituted at the 1-N or 3-C positions.[4,12] However, among the latter methods,

(1) Rodgers, J. D.; Johnson, B. L.; Wang, H.; Greenberg, R. A.; Erickson-Viitanen, S.; Klabe, R. M.; Cordova, B. C.; Reyner, M. M.; Lam, G. N.; Chang, C.-H. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 2919−2924.

(2) See, for example: Brase, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem.* **2002**, *10*, 2415−2437.

(3) Gomtsyan, A.; Bayburt, E. K.; Koenig, J. R.; Lee, C.-H. U.S. Patent Application 2004254188, Dec 16, 2004.

(4) For reviews see: (a) Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 5, p 167. (b) Behr, L. C.; Fusco, R.; Jarobe, C. H. In *Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings*; Wiley, R. H., Ed.; Wiley Int.: New York, 1969; p 28.

(5) Ruechardt, C.; Hassmann, V. *Liebigs Ann. Chem.* **1980**, *6*, 908−927.

(6) For other examples of indazoles synthesis via diazonium salt see: Schumann, P.; Collot, V.; Hommet, Y.; Gsell, W.; Dauphin, F.; Sopkova, J.; MacKenzie, E. T.; Duval, D.; Boulouard, M.; Rault, S. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 1153−1156.

(7) (a) Tono-oka, S.; Tone, Y.; Marques, V. E.; Cooney, D.; Sekikawa, I.; Azuma, I. *Bull. Chem. Soc. Jpn*. **1985**, *58*, 309−315. (b) Shoda, M.; Kuriyama, H. U.S. Patent Application 2003070686, Aug 28, 2003.

(8) (a) Jacobsen, P.; Huber, L. *Chem. Ber*. **1908**, *41*, 660. (b) Ruchardt, C.; Hassmann, V. *Liebigs Ann. Chem.* **1980**, 908−927.

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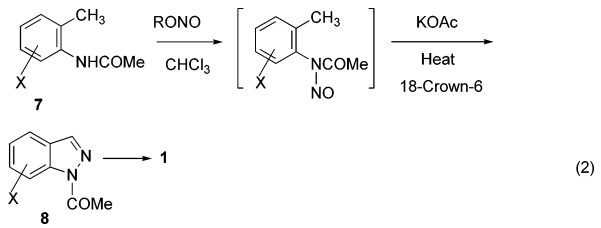
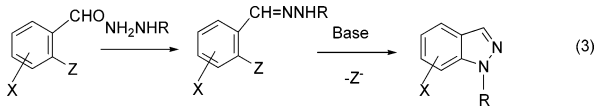


(2)

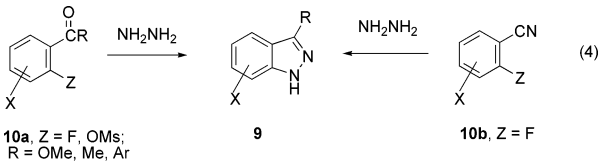
a condensation of ortho-substituted benzaldehydes with hydrazines (eq 3) looked particularly straightforward and attractive



(3)

for the adaptation for the synthesis of indazoles **3** and **4**.

The condensation outlined in eq 3, utilizing nitro as a leaving group (Z = NO_2) was first reported more than a century ago.[13] It was demonstrated that several substituted hydrazones (R ≠ H), which were initially formed in the reactions of *o*-nitrobenzaldehydes with the corresponding hydrazines, could be further converted into the indazoles in the presence of a base under very forcing conditions. Later, this method was adapted by employing the corresponding *o*-fluoro- and *o*-mesyloxy-substituted[14] benzocarbonyl compounds. Several groups reported that various 3-substituted indazoles **9** (R ≠ H, eq 4) could be



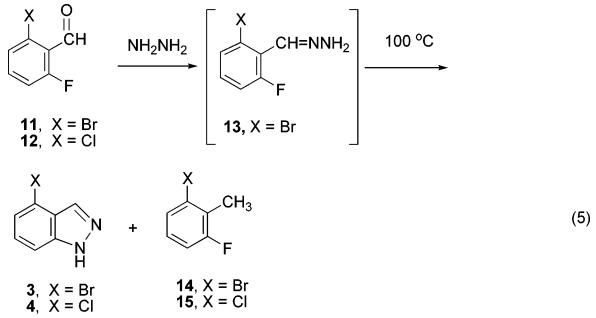
(4)

efficiently prepared via condensations of the corresponding esters of 2-fluorobenzoic acid (**10a**, R = OMe), fluoroaceto, and fluorobenzophenones (**10a**, R = Me, Ar), as well as 2-fluorobenzonitriles **10b**, with hydrazine.[15−18]

Surprisingly though, we could not find any references of similar condensations involving *o*-fluorobenzaldehydes—starting materials required for the preparation of indazoles unsubstituted at the 3-position. The results of our investigation of the latter reaction, which led to the development of a new practical synthesis of indazoles, are provided below.

Results and Discussion

1. Synthesis of 4-Haloindazoles. Our initial investigation into the synthesis of 4-bromo and 4-chloroindazoles (**3**, **4**) via a condensation of the corresponding 6-halo-2-fluorobenzaldehydes **11** and **12** with hydrazine gave fairly promising results. For example, when the reaction of aldehyde **11** with hydrazine hydrate (3 equiv) in the presence of sodium bicarbonate was monitored by HPLC, a fast and quantitative formation of hydrazone intermediate **13** was initially observed (eq 5). Further



(5)

heating of this mixture to 90−100 °C for 5 h resulted in conversion of **13** into an approximately 2:3 mixture of the desired indazole **3** and an unknown side product. The side product was subsequently identified as bromofluorotoluene **14**,[19] apparently resulting from the Wolf−Kishner type reduction of the intermediate hydrazone **13** (eq 5). Similar results were observed with 6-chloro analogue **12**.

As it was generally presumed that the formation of indazoles from ortho-substituted hydrazones proceeded as an intramolecular cyclization (eq 3), we decided to further optimize the reaction conditions for this cyclization using the isolated pure hydrazone **13**. First, we found that a careful selection of a base was critical for minimizing the Wolf−Kishner pathway. Thus, in the presence of bases stronger than sodium bicarbonate (e.g., potassium carbonate, triethylamine) fast and quantitative reduction of hydrazone **13** to toluene **14** was observed. The formation of indazole **3** was only observed in the presence of weak bases (e.g., sodium bicarbonate, pyridine). However, the cyclization of the *isolated* hydrazone **13** proceeded remarkably slower, compared to the described above reaction of the same hydrazone, when it was formed in situ. Even after 72 h at 100 °C, some of the starting hydrazone remained in the mixture. Moreover, the yield of indazole **3** obtained in this experiment was lower than 10%, due to the formation of toluene **14** and other numerous side products. These data suggested that the

(9) The diazotation method generally requires the isolation of a potentially explosive diazonium salt intermediate. The formation and cyclization of the diazonium salt proceed simultaneously under the reaction conditions only in the presence of additional highly electron-withdrawing groups (e.g., nitro): (a) Bartsch, R. A.; Tang, I.-W. *J. Heterocycl. Chem.* **1984**, *21*, 1063. (b) Porter, H. D.; Peterson, W. D. *Org. Synth*. **1955**, *III* (Collective Vol.), 660.

(10) Even the most advanced modification of the Jacobsen reaction remains relatively impractical, as it requires the addition of 0.1 equiv of expensive and toxic crown ether catalyst, employs toxic chloroform as a preferred solvent, and adds a deprotection step to recover the indazole: (a) Beadle, J. R.; Korzeniowski, S. H.; Rosenberg, D. E.; Garcia-Slanga, B. J.; Gokel, G. W. *J. Org. Chem.* **1984**, *49*, 1594−1603. (b) Sun, J.-H.; Teleha, C. A.; Yan, J.-S.; Rodgers, J. D.; Nugiel D. A. *J. Org. Chem.* **1997**, *62*, 5627−5629.

(11) Bromoindazole **3** was obtained as one of the products resulting from the condensation of bromobenzyne with (trimethylsilyl)diazomethane: Shoji, Y.; Hari, Y.; Aoyama, T. *Tetrahedron Lett.* **2004**, *45*, 1769−1771.

(12) Song, J. J.; Yee, N. K. *Tetrahedron Lett.* **2001**, *42*, 2937−2940.

(13) (a) Meyer, V. *Chem. Ber*. **1889**, *22*, 319. (b) Reich, S.; Gaigalian, G. *Chem. Ber*. **1913**, *46*, 2380−2387.

(14) Caron, S.; Vazquez, E. *Synthesis* **1999**, *4*, 588−592.

(15) Cui, J. J.; Araldi, G.-L.; Reiner, J. E.; Reddy, K. M.; Kemp, S. J.; Ho, J. Z.; Siev, D. V.; Mamedova, L.; Gibson, T. S.; Gaudette, J. A.; Minami, N. K.; Anderson, S.; M.; Bradbury, A. E.; Nolan, T. G.; Semple, J. E. *Bioorg. Med. Chem. Lett*. **2002**, *12*, 2925−2930.

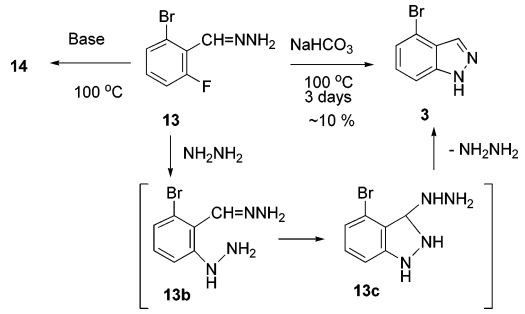
(16) Henke, B. R.; Aquino, C. J.; Birkemo, L. S.; Croom, D. K.; Dougherty, R. W.; Ervin, G. N.; Grizzle, M. K.; Hirst, G. C.; James, M. K.; Johnson, M. F.; Queen, K. L.; Sherrill, R. G.; Sugg, E. E.; Suh, E. M.; Szewczyk, J. W.; Unwalla, R. J.; Yingling, J.; Willson, T. M. *J. Med. Chem.* **1997**, *40*, 2706−2725.

(17) (a) Shutske, G. M.; Allen, R. C.; Forsch, M. F.; Setescak, L. L.; Wilker, J. C. *J. Med. Chem.* **1983**, *26*, 1307−1311. (b) Dehmlow, H.; Aebi, J. D.; Jolidon, S.; Ji, Y.-H.; Mark, E. M.; Himber, J.; Morand, O. H. *J. Med. Chem.* **2003**, *46*, 3354−3370.

(18) Witherington, J.; Bordas, V.; Gaiba, A.; Naylor, A.; Rawlings, A. D.; Slingsby, B. P.; Smith, D. G.; Takle, A. K.; Ward, R. W. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 3059−3062.

(19) Dewar, M. J. S.; Grisdale, P. J. *J. Org. Chem*. **1963**, *28*, 1759−1762.

SCHEME 1

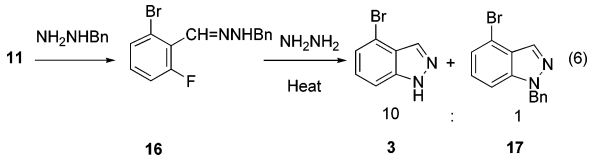


formation of indazoles in reactions of *o*-fluorobenzaldehydes with hydrazine under the investigated set of conditions *did not* proceed via an *intramolecular* cyclization of hydrazone **13**.[20]

In search of an explanation for the above results, we found that the indazole formation from **11** could be facilitated in the presence of excess hydrazine. Indeed, when the isolated hydrazone **13** was added to hydrazine hydrate, which was used as a solvent, heating the solution to 100 °C for only 1 h resulted in consumption of the starting material.

Based on these data we rationalized that the mechanism for the conversion of the *o*-fluorophenylhydrazones into indazoles in the presence of excess hydrazine proceeded by substitution of the aryl fluoride with another molecule of hydrazine, followed by the cyclization of **13b** as outlined in Scheme 1.

According to this mechanism, the hydrazine molecule, which was initially incorporated into the hydrazone fragment of **13**, would be later eliminated as a result of a subsequent cyclization step via aminal **13c** (Scheme 1). To support this proposed mechanism we prepared benzyl-substituted hydrazone **16** and subjected it to the cyclization conditions in hydrazine hydrate (eq 6). As we expected, nonbenzylated indazole **3** was formed



as a major product (the 10:1 ratio of indazole **3** and benzylindazole **17** was determined by HPLC methodology). Importantly, only traces of toluene side product were observed in the reaction mixture (in comparison to the cyclization of **13** which gave 30−40% of reduction product), suggesting that hydrazone **13** was not a major intermediate *in this reaction* and that the indazole formation proceeded in an intramolecular fashion, after the fluoride substitution in **16** (Scheme 1).

As an outcome of the above mechanistic rationalization, we were able to prepare 4-haloindazoles **3** and **4** simply by refluxing the corresponding aldehydes in hydrazine hydrate. Upon the completion of the reaction, the product typically precipitated out during cooling of the crude reaction mixture and was conveniently isolated through filtration. The yields of indazoles **3** and **4** obtained in this reaction were satisfactory (50−60%), however, still negatively affected by the formation of toluenes **14** and **15**, as side products. Upon further optimization of the reaction parameters, we have found that the extent of the reduction could be attenuated by conducting the reaction in etheral solvents such as THF, DME, or dioxane and employing anhydrous hydrazine as a cosolvent. Under these optimized conditions (1:1 THF−98% hydrazine, 70 °C, 15 h) the isolated yields of indazoles **3** and **4** were increased to 80−85%, respectively.

2. Condensation of Other *o*-Fluorobenzaldehydes with Hydrazine. In an attempt to determine the generality of this practical approach, the condensations of several substituted *o*-fluorobenzaldehydes (**18**−**24**) were evaluated using the conditions found optimal for aldehydes **11** and **12**. The selection of the *o*-fluorobenzaldehydes was designed to evaluate both the impact of the substitution pattern and the electronic effect of substituents (eq 7). The results of this study are summarized in

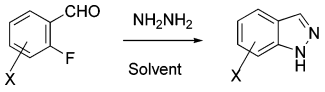


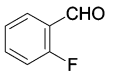
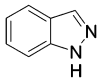
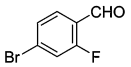
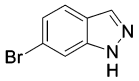
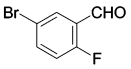
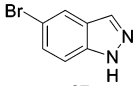
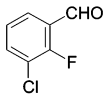
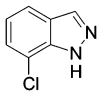
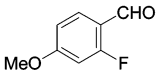
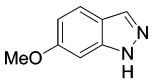
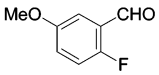
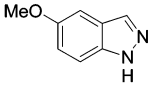
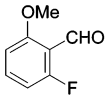
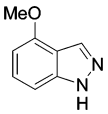
Table 1.

We were pleased to find that the desired indazoles could be obtained in good yields in most of the cases studied. At the same time, the data in Table 1 show that the cyclizations of unsubstituted fluorobenzaldehyde **18** and 5-bromo-2-fluorobenzaldehyde (**20**) gave reduced yields of the corresponding indazoles, whereas 5-methoxy-substituted aldehyde **23** gave only the corresponding toluene reduction product. The lower efficiency of the condensation reaction in the latter examples could be rationalized by considering the effect of substituents on the rates of the two competitive processes—nucleophilic substitution of the fluoride leading to indazole formation and the hydrazone intermediate reduction leading to the toluene. For example, introduction of the electron-donating methoxy substituent in para or ortho positions relative to the carbonyl group (compounds **22**, **24**) would presumably decelerate the hydrazone reduction, while having little effect on the fluoride substitution. At the same, introduction of the methoxy substituent in the para position relative to the fluoride (compound **23**) would deactivate the fluoride substitution, with little effect on the hydrazone reduction rate. Accordingly, the condensation of aldehyde **24** resulted in a high yield of 4-methoxyindazole (**31**), whereas the analogous reaction of aldehyde **23** gave the reduction product only. Although in all studied cases the toluene side products could be conveniently removed from the indazoles by a heptane wash, or simply during the product drying under vacuum, we still sought better control over the reduction pathway to achieve higher yields of indazoles regardless of the substitution.

3. Condensation of 2-Fluorobenzaldehyde *O*-Methyloximes with Hydrazine. The condensation of benzylhydrazone **16** with hydrazine (eq 6) provided important clues for further method development. As noted above, this reaction resulted in replacement of benzylhydrazine and gave nearly exclusively indazole unsubstituted at the 1-N position. These findings allowed us to propose that not only various substituted hydrazones (e.g., **16**) but other appropriately protected aldehydes could be utilized in the condensations with hydrazine for indazoles preparation. Moreover, elimination of the hydrazone intermediate from this new process would avoid the Wolf−Kishner pathway leading to the toluene side products. We thought that easily accessible oximes could be good surrogates to investigate this approach.

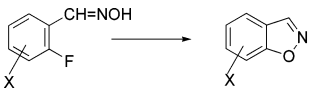
(20) It is possible that intramolecular cyclization of hydrazones with the formation of indazoles still could be accomplished at higher temperatures. In the related study of the intramolecular cyclizations of 2-mesyloxyacetophenones hydrazones (ref 18, eq 4), the indazole formation was observed at temperatures above 130 °C. However, a DSC scan of hydrazone **13** indicated that it underwent highly exothermic decomposition at 140−150 °C, prompting us to set 110 °C as the upper limit for all our experiments.

TABLE 1. Indazole Formation from Benzaldehydes 11, 12, 18−24

Entry	Aldehyde	Product	Isolated Yield (%)
1	**11**	**3**	79 (81)[a]
2	**12**	**4**	82[b]
3	 **18**	 **25**	29 (32)[a, c]
4	 **19**	 **26**	78
5	 **20**	 **27**	45 (48)[a]
6	 **21**	 **28**	74 (77)[a]
7	 **22**	 **29**	47 (72)[a]
8	 **23**	 **30**	0
9	 **24**	 **31**	47

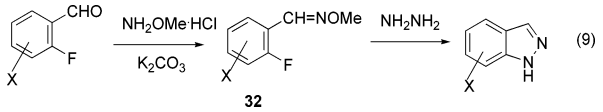
[a] Reaction yield, as determined by HPLC assay. [b] Additionally, toluene **15** was formed in 13% yield (HPLC assay). [c] Additionally, 2-fluorotoluene was formed in 45% yield (HPLC assay).

However, it has been reported that unprotected oximes of substituted 2-fluorobenzaldehydes could undergo a self-cyclization into isoxazoles, as outlined in eq 8.[21]



(8)

The isoxazole side product formation was obviated by using *O*-methyloximes **32** instead of oximes. Compounds **32** could be simply prepared in quantitative yields by reacting the equivalent amounts of fluorobenzaldehydes and methyloxime hydrochloride in the presence of potassium carbonate (eq 9). We were pleased to find that the reaction of 2-fluorobenzaldehyde *O*-methyloxime prepared in this manner with hydrazine cleanly gave indazole, which was isolated in 80% yield (eq 9, X = H) representing a nearly 3-fold yield improvement over



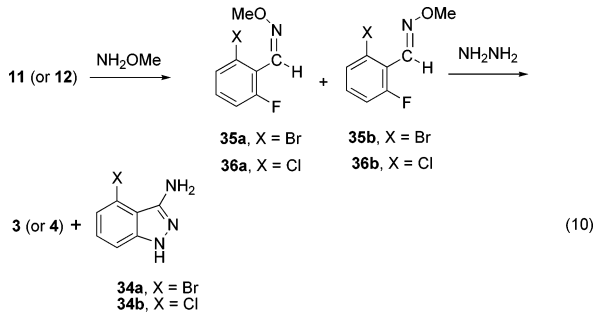
(9)

32

the standard conditions using the hydrazone intermediate (Table 1, entry 3). Adding to the convenience of this procedure, no isolation of the methyloxime intermediate was required before the indazole formation step. The reaction with hydrazine was conducted simply after filtering off the inorganics from the crude oxime solution (vide infra).

In a similar manner, the benzaldehydes referenced in Table 1, as well as 2,6-difluorobenzaldehyde (**39**), were converted into the corresponding methyloximes and, subsequently, indazoles in high yields, as summarized in Table 2. The only exception to this generality was the methyloxime of highly deactivated 5-methoxy-substituted aldehyde **23**, which upon extended reaction time gave only 5% yield of **30**.

Surprisingly, 6-bromo- and 6-chloro-substituted benzaldehydes **11** and **12**, which gave the highest yields of indazoles in the cyclizations via hydrazone intermediate (Table 1, entries 1 and 2), behaved unusually in the cyclization via their requisite methyloxime. It was found that in addition to the corresponding indazoles **3** and **4**, other more polar products (12−14% by HPLC peak area vs **3** or **4**) were formed in these reactions (eq 10).



(10)

These side products were identified as 3-aminoindazoles **34a** and **34b**,[22] respectively. It was also observed that formation of **34** could be related to the increased amounts of the minor *Z*-isomers of oximes **35** or **36** formed during the oximation of aldehydes **11** and **12**, respectively (see Table 2).[23] To confirm that 3-aminoindazoles were indeed formed from the corresponding *Z*-oxime isomers, we attempted the isolation of individual compounds **35a** and **35b**. Although the separation of these isomers via chromatography was not achievable, it was possible to isolate the major *E*-form **35b** (<5% *Z*) by fractional crystallization of the mixture from pentane at 0 °C. The cyclization of this enriched material under the standard conditions resulted in the expected decrease in the yield of **34a**, which dropped to 3% vs **3**, confirming the aminoindazole origination from *Z*-isomer **35a**.

We do not have an explanation for the increased amounts of *Z*-isomers formation in the oximations of aldehydes **11** and **12**. However, a comparison of the oxime ratios listed in Table 2 suggests that this phenomenon is related to the size of the substituent at the 6-position of the aldehyde. Thus, a gradual

(21) Strupczewski, J. T.; Allen, R. C.; Gardner, B. A.; Schmid, B. L.; Stache, U.; Glamkowski, E. J.; Jones, M. C.; Ellis, D. B.; Huger, F. P.; Dunn, R. W. *J. Med. Chem.* **1985**, *28*, 761−769.

(22) Voss, G.; Eichner, S. *J. Prakt. Chem.* **2000**, *342*, 201−204.

(23) The *Z*/*E* ratios of 25:75 and 22:78 were determined for methyloximes **35** and **36** by HPLC methodology. Other investigated methyloximes had less than 10% of *Z*-isomer. Isomers assignment in methyloximes is based on ^{13}C NMR data: Gordon, M. S.; Sojka, S. A.; Krause J. G. *J. Org. Chem.* **1984**, *49*, 97−100.

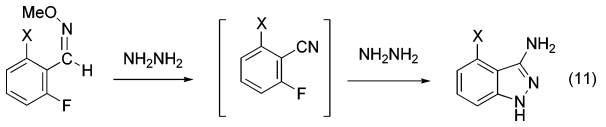
TABLE 2. Conversion of *o*-Fluorobenzaldehydes into the Indazoles via the Methyloxime Method

indazole	X (eq 9)	isolated yield (%)[a]	*Z*/*E* oximes ratio[b]
25	H	80	5/95
26	6-Br	70	6/94
27	5-Br	94	6/94
28	7-Cl	84	6/94
29	6-MeO	69	8/92
30	5-MeO	5[b]	4/96
33	4-F	75	9/91
31	4-MeO	70	15/85
3	4-Br	70 (86/14)[c]	25/75
4	4-Cl	72 (88/12)[d]	22/78

[a] The isolated yields of individual compounds were not optimized. [b] Determined by HPLC methodology. [c] Compounds **3**/**34a** ratio in the reaction mixture determined by HPLC methodology. [d] Compounds **4**/**34b** ratio in the reaction mixture determined by HPLC methodology.

increase in the amounts of *Z*-isomers was observed when the 6-substituent in the benzaldehyde molecule was changed from hydrogen to bromine (Br > Cl > MeO > F > H, see Table 2). The same substituents did not significantly affect the ratio of oxime isomers, if they were placed in other positions in the molecule. Accordingly, we did not observe the formation of any side products with an HLPC peak area higher than 5% in the condensations of the latter oximes (see Table 2).[24]

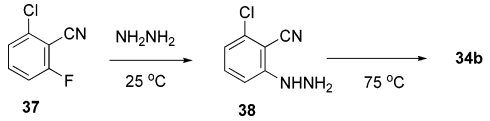
A plausible mechanism for the observed formation of 3-aminoindazoles in the condensations of *Z*-methyloximes with hydrazine is outlined in eq 11.



(11)

This mechanism is based on the reported literature precedents.[14,17] It was also demonstrated that *O*-methyloximes of benzaldehydes, possessing electron-withdrawing groups, could be converted into the corresponding nitriles in the presence of bases as strong as aqueous sodium hydroxide.[25] The selective benzonitrile formation from the *Z*-isomer of oxime under the reaction conditions probably represented a kinetic effect. Relatively faster elimination of methanol from the *Z*-isomer could be explained by the preferred orbital orientation in the elimination transitions state of this isomer, in line with the general stereochemical considerations for the reactions proceeding via an E2 mechanism.[26]

Further support of the mechanism outlined in eq 11 was obtained during monitoring the condensation of oximes **36** with hydrazine by HPLC. While no intermediates were observed in the cyclization of **36b** into **4**, the formation of aminoindazole **34b** clearly proceeded via an intermediate (40% peak area vs **34b** after 1 h; 10% after 2 h; <1%, after 4 h). Although we could not detect the presence of nitrile **37** in this reaction mixture directly, the intermediate was identified as its derivative, hydrazide **38**, by spiking the reference compound into the HPLC sample of the reaction mixture. Hydrazide **38** was in turn isolated from the reaction of nitrile **37** with hydrazine at room temperature (eq 12).[27−29]



(12)

As expected, compound **38** was further converted into indazole **34b** by heating the reaction mixture to 75 °C.

Conclusions

We have established a new practical synthesis of indazoles via reaction of *o*-fluorobenzaldehydes and/or their *O*-methyloximes with excess hydrazine. High yields of indazoles (70−85%) were obtained in the condensations of aldehydes with various substitution patterns with the exception of those possessing electron-donating groups in the 5-position, as well as unsubtituted *o*-fluorobenzaldehyde. The yields of indazoles prepared from the nonoptimal aldehydes were lower due to competitive Wolf−Kishner reduction. This side reaction was effectively eliminated via utilization of *O*-methyloxime derivatives of the aldehydes for the preparation of indazoles in the condensation with hydrazine. All studied aldehydes (with the exception of the poorly reactive 5-methoxy compound) were efficiently converted into the corresponding indazoles using the methyloxime method. A side reaction, resulting in the formation of 3-aminoindazoles, was observed in the experiments with oximes possessing relatively high levels of *Z*-isomers. The aminoindazole side products were selectively formed from *Z*-isomers of these oximes, via the corresponding nitrile intermediates under the reaction conditions.

Finally, we would like to note that condensations of *O*-methyloximes with nucleophiles other than hydrazine could potentially provide a new practical methodology for the preparation of various heterocyclic systems. We will report on this chemistry in a due time.

Experimental Section

General. Commercially available *o*-fluorobenzaldehydes and 2-chloro-6-fluorobenzonitrile (**37**) were used in this study.

Reaction mixtures and isolated products were analyzed by HPLC (Zorbax Rx C8 column, detection at 205 nm). All isolated indazole compounds had an HPLC purity better than 95%. ^{1}H NMR spectra were recorded at 400 MHz; ^{13}C NMR spectra were recorded at 100 MHz.

General Procedure for the Preparation of Indazoles from Fluorobenzaldehydes. Method A. Hydrazine (98%, 10 mL) was added over 5 min to a solution of an aldehyde (10 mmol) in DME (10 mL). The reaction mixture was refluxed for 15 h and concentrated in vacuo to approximately 10 mL. Water (10−20 mL) was added to the mixture. The resulting product precipitate was filtered off and dried in vacuo. Indazoles **3**, **4**, **25**−**29**, and **31** were obtained using this procedure. DME solvent could be replaced with THF or dioxane.

(24) We did not attempt to identify the structures of minor side products formed in these reactions in less than 5% peak area by HPLC methodology.

(25) Hagarty, A. F.; Tuobey, P. J. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1313.

(26) Marchese, G.; Naso, F.; Modena, G. J. *J. Chem. Soc. B* **1968**, 958.

(27) The structure of intermediate **37** was supported by ^{13}C NMR, which showed the presence of a nitrile carbon at 155.1 ppm and the disappearance of ^{13}C−^{19}F coupling.

(28) For examples of halogen displacement with hydrazine in substituted benzonitrile see: (a) Parnell *J. Chem. Soc.* **1959**, 2363. (b) Voss, G.; Eichner, S. *J. Prakt. Chem.* **2000**, *342*, 201−204.

(29) Alternatively, nitrile formation could occur after fluoride substitution with hydrazine. This, however, seems less likely, as a highly electron-donating hydrazide will deactivate the methyloxime group for elimination.

General Procedure for the Preparation of Indazoles from Fluorobenzaldehydes via *O*-Methyloxime Intermediates. Method B. An aldehyde (5 mmol), methylhydroxylamine hydrochloride (0.41 g, 5 mmol), and potassium carbonate (0.76 g, 5.5 mmol) were mixed in DME (10 mL) for 4−5 h at 40 °C. The reaction mixture was filtered, and the filtrate containing the oxime intermediate was concentrated in vacuo to approximately 5 mL. Hydrazine (98%, 5 mL) was added to the concentrated oxime solution, and the mixture was refluxed for 5−25 h, until the reaction was complete per HPLC analysis. The reaction mixture was concentrated in vacuo to approximately 5 mL. Water (10 mL) was added to the mixture. The resulting product precipitate was filtered off and dried in vacuo. Indazoles **3**, **4**, **25**, **27**−**29**, **31**, and **33** were obtained using this procedure.

4-Bromoindazole (3)[7b,11] was obtained in 81% yield by method A: ^{1}H NMR (DMSO-d_6, δ, ppm) 7.28 (t, 1H, J = 7.6 Hz), 7.34 (d, 1H, J = 7.4 Hz), 7.59 (d, 1H, J = 7.5 Hz), 8.05 (s, 1H), 13.46 (s, 1H, −NH).

Attempted preparation of 4-bromoindazole by method B gave a mixture of indazoles **3** and **34a** in 86:14 ratio. The mixture was separated by column chromatography on silica gel eluting with 9:1 heptane−ethyl acetate. Bromoindazole **3** was eluted first and isolated in 70% yield.

3-Amino-4-bromoindazole (34a) was obtained in 10% yield: ^{1}H NMR (DMSO-d_6, δ, ppm) 5.18 (s, 2H, −NH), 7.05−7.19 (m, 2H), 7.29 (d, 1H, J = 7.8 Hz), 11.88 (s, 1H, −NH). ^{13}C NMR (DMSO-d_6, δ, ppm) 109.0 (CH), 111.5 (C), 113.1 (C), 120.7 (CH), 127.0 (CH), 141.8 (C), 147. 7 (C). Anal. Calcd for $C_7H_6BrN_3$: C, 39.65; H, 2.85; N, 19.82. Found: C, 39.75; H, 2.80; N, 19.36.

4-Chloroindazole (4)[5,7a] was obtained in 82% yield by method A: ^{1}H NMR ($CDCl_3$, δ, ppm) 7.15 (d, 1H, J = 7.4 Hz), 7.30 (t, 1H, J = 7.4 Hz), 7.40 (d, 1H, J = 7.5 Hz), 8.16 (s, 1H), 10.61 (s, 1H, −NH).

Attempted preparation of 4-chloroindazole by method B gave a mixture of indazoles **3** and **34b** in 88:12 ratio. The mixture was separated by column chromatography on silica gel eluting with 9:1 heptane−ethyl acetate. Chloroindazole **3** was eluted first and isolated in 72% yield.

3-Amino-4-chloroindazole (34b)[26] was obtained in 8% yield: ^{1}H NMR (methanol-d_4, δ, ppm) 5.18 (s, 2H, −NH), 7.05−7.19 (m, 2H), 7.29 (d, 1H, J = 7.8 Hz), 11.88 (s, 1H, −NH). ^{13}C NMR (methanol-d_4, δ, ppm) 109.0 (CH), 111.5 (C), 113.1 (C), 120.7 (CH), 127.0 (CH), 141.8 (C), 147.7 (C).

Indazole (25) was obtained in 29% yield by method A and 80% yield by method B: ^{1}H NMR (DMSO-d_6, δ, ppm) 7.09 (t, 1H, J = 7.5 Hz), 7.33 (t, 1H, J = 7.5 Hz), 7.52(d, 1H, J = 8.4 Hz), 7.75 (d, 1H, J = 8.1 Hz), 8.05 (s, 1H), 13.01 (s, 1H, −NH).

5-Bromoindazole (27)[31] was obtained in 45% yield by method A and 94% yield by method B: ^{1}H NMR ($CDCl_3$, δ, ppm) 7.38 (d, 1H, J = 8.8 Hz), 7.47 (dd, 1H, J = 1.7, 8.7 Hz), 7.90 (dd, 1H, J = 0.9, 1.7 Hz), 8.01 (d, 1H, J = 0.9 Hz), 10.08 (s, 1H, −NH).

6-Bromoindazole (26)[32] was obtained in 78% yield by method A and 70% yield by method B: ^{1}H NMR (DMSO-d_6, δ, ppm) 7.24 (d, 1H, J = 8.5 Hz), 7.74 (d, 1H, J = 8.5 Hz), 7.78 (s, 1H), 8.11 (s, 1H), 13.18 (s, 1H, −NH). ^{13}C NMR (DMSO-d_6, δ, ppm) 112.2 (CH), 118.9 (C), 121.3 (C), 121.9 (CH), 122.9 (CH), 133.3 (CH), 140.1 (C).

7-Chloroindazole (28)[32] was obtained in 74% yield by method A and 84% yield by method B: ^{1}H NMR ($CDCl_3$, δ, ppm) 7.12 (t, 1H, J = 7.9 Hz), 7.38 (d, 1H, J = 7.5 Hz), 7.66 (d, 1H, J = 7.9 Hz), 8.12 (s, 1H).

6-Methoxyindazole (29)[6] was obtained in 72% yield by method A and in 69% yield by method B: ^{1}H NMR ($CDCl_3$, δ, ppm) 3.86 (s, 3H), 6.81−6.84 (m, 2H), 7.60 (d, 1H, J = 8.7 Hz), 7.97 (s, 1H), 8.16 (s, 1H).

4-Methoxyindazole (31)[7a] was obtained in 47% yield by method A and 70% yield by method B: ^{1}H NMR ($CDCl_3$, δ, ppm) 3.97 (s, 3H), 6.48 (d, 1H, J = 7.7 Hz), 7.07 (d, 1H, J = 7.6 Hz), 7.29 (t, 1H, J = 7.7 Hz), 8.16 (s, 1H), 10.48 (s, 1H).

4-Fluoroindazole (33)[30] was obtained in 75% yield by method B: ^{1}H NMR ($CDCl_3$, δ, ppm) 6.80 (m, 1H), 7.28−7.32 (m, 2H), 8.16 (s, 1H), 10.5 (s, 1H, −NH).

Bromo-6-fluorobenzaldehyde Hydrazone (13). Bromofluorobenzaldehyde **11** (2.0 g, 10 mmol) was added to a magnetically stirred mixture of hydrazine hydrate (∼55% in water, 2.0 g) and toluene (10 mL) over 0.5 h at 50 °C. After additional 1 h at 50 °C the mixture was cooled to room temperature and diluted with water (5 mL). The organic layer was separated and concentrated to dryness in vacuo. The residue was slurried in heptane (30 mL). Filtration and drying (40 °C, vacuum) gave hydrazone **13** (1.83 g, 91%): ^{1}H NMR (DMSO-d_6, δ, ppm) 7.13−7.27 (m, 2H), 7.31 (s, 2H, $-NH_2$), 7.42−7.49 (m, 1H), 7.79 (s, 1H, −NH). ^{13}C NMR (DMSO-d_6, δ, ppm) 115.3 (d, CH, J = 22.2 Hz), 121.7 (d, C, J = 4.2 Hz), 123.3 (d, C, J = 13.1 Hz), 128.3 (d, CH, J = 3.4 Hz), 128.6 (d, CH, J = 9.4 Hz), 131.1 (d, CH, J = 4.3 Hz), 158.8 (d, C, J = 254 Hz). Anal. Calcd for $C_7H_6BrFN_2$: C, 38.74; H, 2.79; N, 12.91. Found: C, 38.82; H, 2.76; N, 12.70.

Reduction of Bromofluorobenzaldehyde Hydrazone 13. 2-Bromo-6-fluorotoluene (14). A mixture of hydrazone **13** (0.22 g, 1 mmol), potassium carbonate (0.28 g, 2 mmol), hydrazine hydrate (∼55%, 1 mL), and DMA (1 mL) was heated to 100 °C for 1 h under nitrogen atmosphere. The mixture was cooled to room temperature and diluted with hexane (2 mL) and water (3 mL). The hexane layer was separated and washed with water (2 × 2 mL). Careful evaporation of the hexane solution in vacuo gave bromofluorotoluene **14**[19] (0.15 g, 81%): ^{1}H NMR ($CDCl_3$, δ, ppm) 2.33 (s, 3H), 6.91−7.08 (m, 2H), 7.32 (d, 1H, J = 7.8 Hz).

2-Bromo-6-fluorobenzaldehyde Benzylhydrazone (16). Benzylhydrazine dihydrochloride (0.98 g, 5 mmol) and sodium hydroxide (0.6 g, 15 mmol) were mixed in THF (5 mL) for 10 h. The mixture was filtered, and the filtrate containing benzylhydrazine was combined with bromofluorobenzaldehyde **11** (0.97 g, 4.8 mmol). After 2 h at room temperature the mixture was concentrated to dryness in vacuo. The residue was slurried in heptane (30 mL). Filtration and drying (40 °C, vacuum) gave benzylhydrazone **16** (1.35 g, 92%): ^{1}H NMR ($CDCl_3$, δ, ppm) 4.46 (s, 2H), 6.99−7.08 (m, 2H), 7.24−7.41 (m, 6H), 7.64 (s, 1H). ^{13}C NMR ($CDCl_3$, δ, ppm) 52.8 (CH_2), 115.3 (d, CH, J = 22.6 Hz), 123.1 (C), 123.5 (d, C, J = 23 Hz), 127.3 (CH), 127.9 (2C, CH), 128.38 (2C, CH), 128.42 (CH), 128.5 (CH), 130.5 (d, CH, J = 3.8 Hz), 137.0 (C), 159.8 (d, C, J = 255 Hz).

Reaction of Bromofluorobenzaldehyde Benzylhydrazone 16 with Hydrazine. Hydrazine (98%, 1 mL) was added to a solution of benzylhydrazone **16** (0.31 g, 1 mmol) in THF (1 mL). The reaction mixture was refluxed for 15 h and cooled to room temperature.

A 10:1 ratio of bromoindazole **3** and 1-benzylbromoindazole **17** was determined by HPLC methodology.

1-Benzyl-4-bromoindazole (17). A solution of bromoindazole **3** (1.0 g, 5 mmol), benzylbromide (0.9 g, 5.5 mmol), and potassium *tert*-butoxide (0.59 g, 5.3 mmol) in DMF (5 mL) was mixed at 25 °C for 1 h. The mixture was diluted with heptane (10 mL) and water (20 mL). The organic layer was separated, washed with potassium dihydrogen phosphate solution (10% in water, 10 mL), and concentrated in vacuo. The resulting 55:45 mixture of 1- and 2-benzylated indazoles was separated by column chromatography on silica gel eluting with 5:1 heptane−ethyl acetate; the 1-N isomer eluted last. Concentration of the desired fractions gave benzylbromoindazole **17** (0.57 g, 40%): ^{1}H NMR ($CDCl_3$, δ, ppm) 5.56 (s, 2 H), 7.10−7.18 (m, 3H), 7.23−7.32 (m, 5H), 8.04 (s, 1H). ^{13}C NMR ($CDCl_3$, δ, ppm) 53.51 (CH_2), 108.3 (CH), 114.5 (C), 123.24 (CH), 125. 2 (C), 126.8 (2C, CH), 126.9 (CH),128.5 (2 C, CH),

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(31) Boulton, B. E.; Coller, B. A. W. *Aust. J. Chem.* **1974**, *27*, 2343−2347.
(32) Ruchardt, C.; Hassmann, V. *Synthesis* **1955**, 375.

133.2 (CH), 136.0 (C), 139.7 (C). Anal. Calcd for $C_{14}H_{11}BrN_2$: C, 58.56; H, 3.86; N, 9.76. Found: C, 58.63; H, 3.73; N, 9.41.

2-Bromo-6-fluorobenzaldehyde *O*-Methyloxime (35). The oxime solution was prepared according to the above method B. It was concentrated in vacuo, and the residue was chromatographed on silica gel (eluent 10:1 heptane−ethyl acetate) to give pure oxime **35** as a 25:75 mixture of *Z*/*E* isomers as determined by ^{1}H NMR. Anal. Calcd for C_8H_7BrFNO: C, 41.41; H, 3.04; N, 6.04. Found: C, 41.44; H, 2.69; N, 6.07. The *E*-isomer (**35b**, *E*/*Z* > 95 : 5) was obtained by crystallization of the mixture from pentane at 0 °C: ^{1}H NMR ($CDCl_3$, δ, ppm) 4.02 (s, 3H), 7.08 (m, 1 Hz), 7.17 (dt, 1H, J = 5.4, 8.2 Hz), 7.40 (d, 1H, J = 7.9 Hz), 8.28 (s, 1H). ^{13}C NMR ($CDCl_3$, δ, ppm) 62.5 (CH_3), 115.4 (d, CH, J = 22.2 Hz), 120.1 (d, C, J = 14.5 Hz), 123.9 (C), 128.6 (CH), 130.6 (d, CH, J = 9.4 Hz), 144.0 (CH), 160.1 (d, C, J = 257 Hz). For *Z*-isomer **35a**: ^{1}H NMR ($CDCl_3$, δ, ppm) 3.95 (s, 3H), 7.05 (m, 1H), 7.20 (dt, 1H, J = 5.8, 7.9 Hz), 7.36 (d, 1H, J = 7.9 Hz), 8.28 (s, 1H). ^{13}C NMR ($CDCl_3$, δ, ppm) 62.5 (CH_3), 114.4 (d, CH, J = 22 Hz), 121.8 (d, C, J = 14.5 Hz), 122.1 (C), 127.8 (CH), 130.9 (d, CH, J = 9.0 Hz), 140.0 (CH), 159.0 (d, C, J = 254 Hz).

2-Chloro-6-fluorobenzaldehyde *O*-Methyloxime (36). The oxime solution was prepared according to the method B. It was concentrated in vacuo, and the residue was chromatographed on silica gel (eluent 10:1 heptane−ethyl acetate) to give pure oxime **36** as a 22:78 mixture of *Z*/*E* isomers as determined by ^{1}H NMR. For the *E*-isomer (**36b**): ^{1}H NMR ($CDCl_3$, δ, ppm) 4.02 (s, 3H), 6.93−7.09 (m, 1H), 7.17−7.31 (m, 2H), 8.32 (s, 1H). ^{13}C NMR ($CDCl_3$, δ, ppm) 62.5 (CH_3), 114.7 (d, CH, J = 23 Hz), 118.7 (d, C, J = 14 Hz), 125.4 (CH), 130.2 (d, CH, J = 9.0 Hz), 134.5 (C), 142.1 (CH), 160.3 (d, C, J = 257 Hz). Anal. Calcd for C_8H_7ClFNO: C, 51.22; H, 3.76; N, 7.47. Found: C, 51.40; H, 3.86; N, 7.30.

2-Chloro-6-hydrazidobenzonitrile (38). Hydrazine (98%, 5 mL) was added over 15 min to a solution of 2-chloro-6-fluorobenzonitrile (0.78 g, 5 mmol) in THF (5 mL) while maintaining the internal temperature below 30 °C. After an additional 0.5 h at room temperature the THF layer was separated and concentrated to dryness in vacuo maintaining the internal temperature below 30 °C to give hydrazide **38** (0.75 g, 90%): ^{1}H NMR (DMSO-d_6, δ, ppm) 4.37 (s, 2 H), 6.73 (d, 1H, J = 7.7 Hz), 7.17 (d, 1H, J = 8.6 Hz), 7.38 (t, 1H, J = 8.3 Hz), 7.64 (s, 1H). ^{13}C NMR (DMSO-d_6, δ, ppm) 91.9 (C), 110.2 (CH), 114.76 (C), 115.6 (CH), 134.0 (CH), 134.7 (C), 155. 1 (C). Anal. Calcd for $C_7H_6ClN_3$: C, 50.17; H, 3.61; N, 25.07. Found: C, 49.78; H, 3.54; N, 24.97.

Heating of the above reaction mixture to 75 °C for 1 h resulted in the quantitative conversion of intermediate **38** into aminoindazole **34b**, as determined by HPLC methodology.

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