Construction of 1*H*-indazoles from *ortho*-aminobenzoximes by the Mitsunobu reaction

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PII: S0040-4039(19)30666-5
DOI: https://doi.org/10.1016/j.tetlet.2019.07.020
Reference: TETL 50929

To appear in: *Tetrahedron Letters*

Received Date: 3 June 2019
Revised Date: 1 July 2019
Accepted Date: 8 July 2019

Please cite this article as: Conlon, I.L., Konsein, K., Morel, Y., Chan, A., Fletcher, S., Construction of 1*H*-indazoles from *ortho*-aminobenzoximes by the Mitsunobu reaction, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.07.020

Highlights

- The synthesis of 1*H*-indazoles from *ortho*-aminobenzoximes by Mitsunobu chemistry
- Secondary amines are suitable substrates, as well as Boc-activated primary amines
- Simple access to N^1-protected, or N^1-alkylated 1*H*-indazoles
- 1*H*-indazoles may be prepared with or without substitution at the 3-position
- The chemistry is compatible with several functional groups

Graphical Abstract

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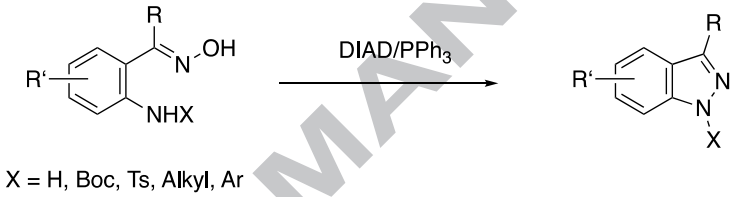

X = H, Boc, Ts, Alkyl, Ar

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Tetrahedron Letters
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Construction of 1*H*-indazoles from *ortho*-aminobenzoximes by the Mitsunobu reaction.

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
1*H*-indazole
Mitsunobu
oxime
cyclodehydration

ABSTRACT

Recently, there has been an upsurge in the occurrence of the indazole motif in drug discovery. Accordingly, newer, milder and more efficient routes towards their synthesis have emerged in the literature. We recently reported the Mitsunobu-triggered cyclodehydration of salicylaldoximes to transient 1,2-benzisoxazoles, and salicylhydroxamic acids to their corresponding 3-hydroxybenzisoxazoles. We hypothesized that the likewise cyclization of *ortho*-aminobenzoximes should deliver the corresponding 1*H*-indazoles. Indeed, secondary amines afforded the predicted N^1-substituted 1*H*-indazoles, and primary amines, after activation with a Boc group, furnished the N^1-Boc 1*H*-indazoles in good to excellent yields. This work further expands the chemical repertoire of the Mitsunobu reaction, representing its unprecedented use in the construction of the 1*H*-indazole nucleus.

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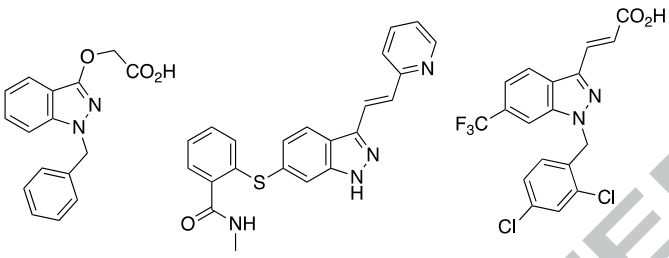
1*H*-Indazoles are incredibly rare in nature but the diverse pharmacological properties imparted to molecules containing this nucleus has catapulted them firmly into the drug designer's toolkit. Indeed, molecules presenting the 1*H*-indazole motif have featured in the development of drugs spanning a range of pathophysiologies, such as inflammation (benzadac, **1**) and renal cell carcinoma (axitinib, **2**), as well as towards the discovery of a male contraceptive (gamendazole, **3**).[1-4] Traditional routes to 1*H*-indazoles involve severe and/or inconvenient conditions,[5,6] for example diazotization, or suffer from poor functional group tolerance.[7] Given the significance of 1*H*-indazoles in medicinal chemistry,[1,2] it is becoming increasingly important to develop milder routes to their synthesis that are compatible with a range of functional groups.

Fig 1. Drug molecules featuring a 1*H*-indazole motif.

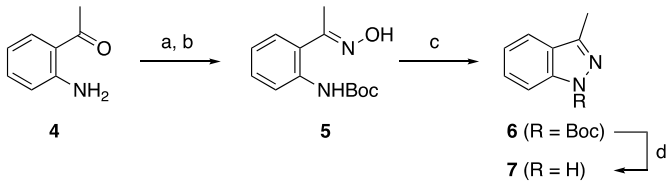
Towards this end, there have been several reports of alternative strategies to access 1*H*-indazoles. Methods include iodine-[8] or PIFA-mediated[9] C-H amination of aryl hydrazones, although yields may be poor or moderate at best, cyclizations of *o*-haloaryl hydrazones, but this requires the *o*-haloaryl aldehyde/ketone,[10] as well as metal-catalyzed C-H activations of various precursors, including imidate esters and NH imines with nitrosoarenes.[11] In addition, CsF-mediated 1,3-dipolar cycloadditions with an α-substituted diazomethylphosphonates and arynes also affords 1*H*-indazoles.[12] A mild procedure was published in 2008 wherein the *in situ O*-mesylation of *ortho*-aminobenzoximes results in a transient intermediate that cyclizes to the 1*H*-indazole nucleus.[13] More recently, Manna and colleagues effected the cyclodehydration of *ortho*-aminobenzoximes to 1*H*-indazoles with the highly electrophilic triphenylphospine-I_2 system,[14] which is a commonly employed ring-closing strategy employed in the synthesis of oxazoles, for example.[15] Given these reports, we considered that the Mitsunobu reaction might effect the same transformation, offering another mild synthesis of 1*H*-indazoles. Indeed, we recently utilized the Mitsunobu reaction to effect the heterocyclization of salicylhydroxamic acids into 3-hydroxybenzisoxazoles,[16] as well as salicylaldoximes into salicylonitriles via *in situ*-generated 1,2-benzisoxazoles.[17]



bendazac, **1** axitinib, **2** gamendazole, **3**

The Mitsunobu reaction is a mild and essentially neutral alkylation, with clean inversion, of an acidic (pro)nucleophile, whose pK_a should be around 12 or lower, such as a carboxylic acid, phenol or sulfonamide with a primary or secondary alcohol.[18-20] A remarkably versatile reaction, it has been employed in the construction of C-O, C-N, C-S as well as C-C bonds.[18-20] Due to its mildness, the Mitsunobu reaction is compatible with a wide range of functional groups. The reaction typically involves an azodicarboxylate, such as diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD), and a phosphine, usually triphenylphosphine. The phosphine reacts with DEAD/DIAD in a phospha-Michael reaction to generate a betaine intermediate, which is the key species that promotes the reaction between the (pro)nucleophile and the alcohol.

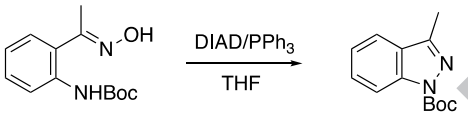
According to the pK_a rule, a primary aromatic amine is unable to engage in the Mitsunobu reaction because its pK_a is too high. Therefore, we elected to reduce the pK_a of the amino functionality by transforming it into a Boc-protected carbamate, which we have observed likewise activates an analogous 2-aminopyrimidine derivative to Mitsunobu chemistry.[21] Briefly, Boc protection of 2'-aminoacetophenone (**4**) was achieved with Boc_2O in hot EtOH; crucially, base was excluded from the reaction mixture to prevent the undesired formation of the corresponding 4-methylene-3,1-benzoaxin-2-one.[22] The requisite oxime functional group was next installed by treatment with hydroxylamine.HCl in pyridine to deliver **5** almost exclusively as the (*E*)-isomer, wherein the hydroxyl and NHBoc are distal to each other; only a trace amount of the readily separable (*Z*)-isomer was observed, consistent with the literature.[13] Pleasingly, treatment of **5** with 1.2 eq of PPh_3 and DIAD effected cyclization to the desired indazole **6** in 65% isolated yield with the mass balance being unreacted starting material. After some experimentation (see Table 1), we arrived at optimal reaction conditions of 2 eq PPh_3 and 2 eq DIAD at 60 °C for 4 h. Note that extending the reaction time from 4 h to 16 h had no benefit to the yield of the indazole (compare entries 5 and 6), likely owing to decomposition of the intermediate betaine. Activation of an oxime's hydroxy can result in its conversion to the corresponding amide or nitrile via the Beckmann rearrangement[23] or, in the case of oximes with α-protons, to the α-aminoketone via the Neber rearrangement.[24] However, the almost-quantitative yield of **6** (entry 6) suggests little or no such rearrangements occurred. Therefore, these conditions were then applied to a range of *N*-Boc-activated *ortho*-aminobenzoximes, and the yields are presented in Table 2.



Scheme 1. a) Boc_2O, EtOH, 50 °C, 48 h; (b) $NH_2OH.HCl$, pyridine; (c) DIAD, PPh_3, THF, 60 °C, 4 h; (d) TFA/CH_2Cl_2, RT, 1 h.

The Mitsunobu reaction was successful with the aldoxime in entry 2 (Table 2), generating the anticipated 3-unsubstituted 1*H*-indazole; the moderate yield was due largely to incomplete consumption of the starting material as no significant by-products were observed. In contrast, Stambuli's conditions led to the dehydration of their analogous aldoxime to the corresponding nitrile.[13] A variety of ketoximes wherein the NHBoc and hydroxyl were distal to one another (entries 3 – 10) – all of which happened to be the (*E*)-isomers were then treated with DIAD and PPh_3; all cyclized in good to excellent yields to the corresponding 1*H*-indazoles. However, the (*Z*)-oxime in entry 11, isomeric to the successful reaction in entry 10, failed to deliver any 1*H*-indazole, indicating that the NHBoc and hydroxyl must be distal to each other for the reaction to proceed.

Table 1. Optimization of the Mitsunobu-triggered cyclodehydration. [a]isolated yield after purification by flash column chromatography



Entry	DIAD (eq.)	Time (h)	Temp. (°C)	Yield (%)[a]
1	1.2	16	25	65
2	2	16	25	77
3	2	16	40	78
4	2	16	50	88
5	2	16	60	95
6	2	4	60	95
7	2	2	60	78

Deprotection of the Boc group of **6** proceeded smoothly and quantitatively with a 1:1 mixture of TFA/CH_2Cl_2, or 4 M HCl/dioxane in under 1 h at RT to furnish **7**. To our surprise, unprotected 1*H*-indazole **7** could also be generated by conducting the Mitsunobu reaction on the non-Boc-protected/activated analogue of **5**, albeit in low yield (Table 3, entry 1), highlighting the significance of the activating group. We surmise this unexpected Mitsunobu reaction was promoted by the close proximity of the activated oxime hydroxyl. Replacement of DIAD with azodicarbonyl dimorpholide (ADDM), which can tolerate less acidic pronucleophiles and has the added benefit of excellent water solubility,[19,25] did not improve the yield. The finding in entry 1 motivated us to apply the optimized reaction conditions to a range of secondary anilines (entry 2). Pleasingly, (unactivated) secondary anilines afforded high yields of the N^1-substituted 1*H*-indazoles, although the hindered *N*-isopropyl oxime (entry 5) did not react. The *N*-aryl oxime in entry 6 cyclized efficiently under the optimized conditions, which is especially noteworthy as alternative, newer 1*H*-indazole synthetic strategies either do not report on such oximes or report that the chemistry was unsuccessful.[13,14] The tosylated substrate yielded a mixture of products.

The proposed mechanism for the Mitsunobu-triggered cyclodehydration is given in Scheme 2. Upon the standard activation of the oxime's hydroxyl group, here playing the role of the alcohol, and deprotonation of the pronucleophile, intermediate **8** is generated. The aniline nitrogen then attacks the oxime nitrogen, displacing the activated alcohol in a *5-exo-trig* heterocyclization that is allowed by Baldwin's rules. This mechanism is also consistent with the observation that the (*Z*)-oxime (Table 2, entry 11) did not afford any of the corresponding 1*H*-indazole because (a) the hydroxyl of the oxime is especially hindered, rendering its activation difficult and (b) the oxime nitrogen is sterically inaccessible and so the cyclization reaction is not possible under these conditions.

Table 2. Substrate scope for Mitsunobu reaction with NHBoc oximes. [a]Reagents and conditions: The oxime (1 eq) is dissolved in anhydrous THF (0.1 M), then PPh_3 (2 eq) and DIAD (2 eq) are added. The reaction is heated at 60 °C for 4 h; [b]isolated yield after purification by flash column chromatography; [c]contaminated with DIAD-H_2, yield determined by NMR.

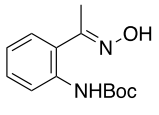
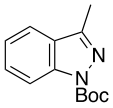
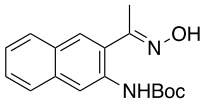
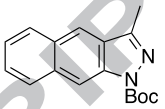
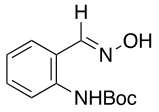
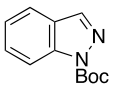
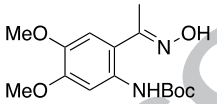
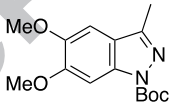
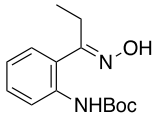
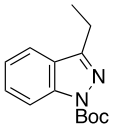
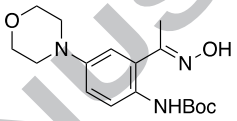
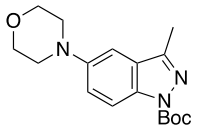
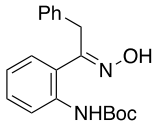
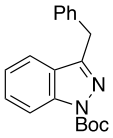
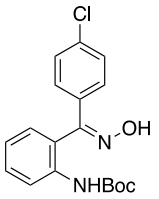
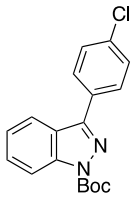
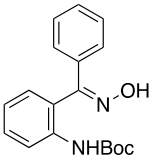
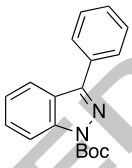
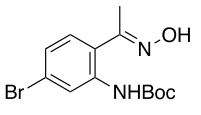
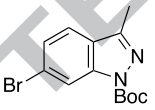
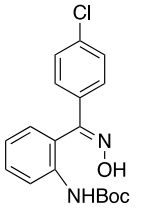
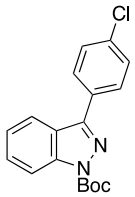
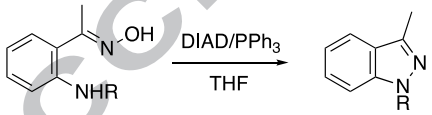
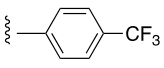
Entry	Oxime	1*H*-Indazole	Yield (%)[b]	Entry	Oxime	1*H*-Indazole	Yield (%)[b]
1			95	7			94
2			68	8			70
3			84	9			82
4			79	10			77
5			74[c]				
6			97	11			0

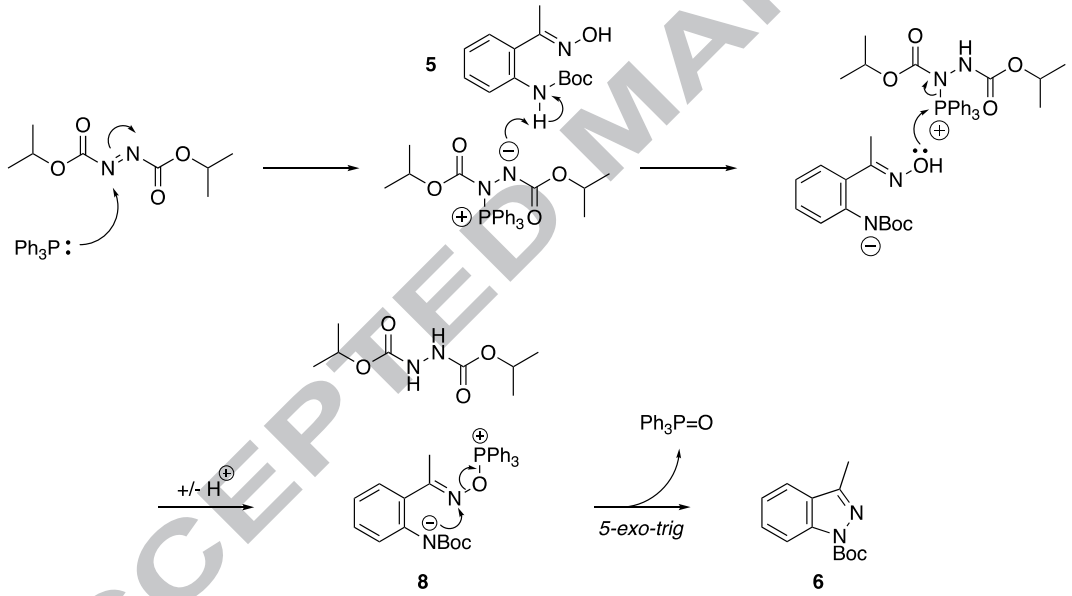
Table 3. Substrate scope for Mitsunobu reaction with NHR oximes utilizing optimized reaction conditions. [a]Isolated yield; [b]contaminated with DIAD-H_2, yield determined by ^{1}H NMR; [c]ADDM substituted for DIAD.



Entry	R	Yield (%)[a]
1	—H	29[b]
2	—H	11[c]
3	—Me	82[b]
4	—allyl	71
5	—isopropyl	0
6		80
7	—Ts	34

Conclusions

In summary, we have further expanded the utility of the Mitsunobu reaction to include the construction of 1*H*-indazoles from *ortho*-aminobenzoximes. Primary amines required pre-activation with a Boc group to deliver the N^1-Boc protected 1*H*-indazoles in good to excellent yields, whilst secondary amines furnished N^1-substituted 1*H*-indazoles directly. The chemistry exhibits a strict geometric criterion – the amino group and hydroxyl must be distal to each other. We proposed a mechanism consistent with these observations wherein the cyclization step is a *5-exo-trig* reaction that is permitted by Baldwin's rules. This chemistry provides not only an alternative to several of the approaches to 1*H*-indazoles that have emerged recently but distinct advantages as well. First, the ability to prepare 3-unsubstituted 1*H*-indazoles from the precursor aldoxime opens the door to a variety of chemical transformations at the 3-position, including halogenation and acylation. Second, this methodology permits the synthesis of 1*H*-indazoles substituted at the N1 position with aryl groups. Since Mitsunobu chemistry is mild and occurs under essentially neutral conditions, it is predicted that this work will become a popular strategy in the synthesis of the 1*H*-indazole motif.



Scheme 2. Proposed mechanism for construction of the 1*H*-indazole nucleus under Mitsunobu conditions.

Acknowledgements

We thank the University of Maryland School of Pharmacy for financially supporting this research.

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26. Preparation of (*E*)-*N*-Boc-*ortho*-aminobenzoxime: 2-aminoacetophenone (**4**; 1 g, 7.40 mmol, 1 eq) was heated at 50°C with Boc_2O (1.78 g, 8.14 mmol, 1.1eq) in ethanol (12 mL) for 48 h. TLC confirmed the reaction was complete. The reaction mixture was concentrated to dryness, reconstituted in CH_2Cl_2, adsorbed to silica gel, then purified by flash column chromatography (eluent: Hex/EtOAc, 2:1) to deliver *tert*-butyl (2-acetylphenyl)carbamate (1.5 g, 88%): δ_H (400 MHz, $CDCl_3$) 10.95 (s, 1H, NH), 8.47 (d, 1H, Ar, J = 8.8 Hz), 7.86 (d, 1H, Ar, J = 7.6 Hz), 7.52 (t, 1H, Ar, J = 7.6 Hz), 7.26 (s, 1H, Ar), 7.03 (t, 1H, Ar, J = 8.0 Hz), 2.65 (s, 3H, $COCH_3$), 1.52 (s, 9H, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 202.2, 153.1, 141.8, 134.9, 131.6, 121.4, 120.9, 119.1, 80.5, 28.5, 28.3. *tert*-Butyl (2-acetylphenyl)carbamate (400 mg, 1.70 mmol, 1 eq) were refluxed with $NH_2OH.HCl$ (472 mg, 6.80 mmol, 4 eq) and pyridine (1.51 mL, 18.7 mmol, 11 eq) in methanol (6 mL) overnight. The reaction was then cooled to room temperature, and partitioned between 1M HCl and EtOAc. The organic layer was collected, and the aqueous was extracted once more with further EtOAc. The combined organic layers were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was adsorbed onto silica gel from CH_2Cl_2, then purified by flash column chromatography, eluting with Hex/EtOAc, 2:1 to furnish *tert*-butyl (*E*)-(2-(1-(hydroxyimino)ethyl)phenyl)carbamate **5** (91%): δ_H (400 MHz, DMSO-d_6) 8.05 (d, 1H, Ar, J = 8.8 Hz), 7.50 (d, 1H, Ar, J = 8 Hz), 7.32 (t, 1H, Ar, J = 8.4 Hz), 7.09 (t, 1H, Ar, J = 7.6 Hz), 2.21 (s, 3H, CH_3), 1.47 (s, 9H, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 183.3, 157.9, 153.2, 137.2, 129.7, 128.4, 121.9, 119.8, 80.2, 28.4, 13.4.
27. Typical Mitsunobu procedure: To a solution of *tert*-butyl (*E*)-(2-(1-(hydroxyimino)ethyl)phenyl)carbamate (125 mg, 0.5 mmol, 1 eq) in anhydrous THF (5 mL) were added PPh_3 (262 mg, 1 mmol, 2 eq) and DIAD (197 µL, 1 mmol, 2 eq). The reaction was heated at 60 °C for 4 h. The solvent was removed *in vacuo*, the crude residue was adsorbed to silica gel from CH_2Cl_2, and then purified by flash column chromatography (eluent: Hex/EtOAc, 3:1) to afford *tert*-butyl 3-methyl-1*H*-indazole-1-carboxylate **6** (110 mg, 95%): δ_H (400 MHz, $CDCl_3$) 8.07 (d, 1H, Ar, J = 7.6 Hz), 7.60 (d, 1H, Ar, J = 8 Hz), 7.47 (t, 1H, Ar, J = 7.6 Hz), 7.26 (t, 1H, Ar, J = 8 Hz), 2.56 (s, 3H, CH_3), 1.69 (s, 9H, $C(CH_3)_3$); 149.3, δ_H (100 MHz, $CDCl_3$) 149.3, 148.5, 140.1, 128.8, 125.9, 123.2, 120.3, 114.6, 84.5, 28.2, 12.3.

Graphical Abstract

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Construction of 1*H*-indazoles from *ortho*-aminobenzoximes by the Mitsunobu reaction.

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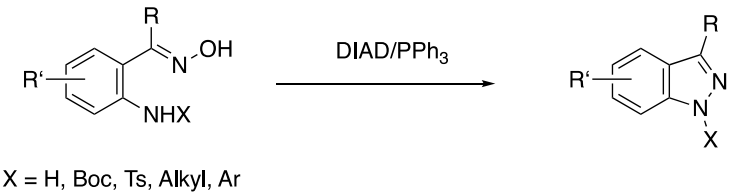

X = H, Boc, Ts, Alkyl, Ar

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