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Claimed 2,1-Benzisoxazoles Are Indazalones

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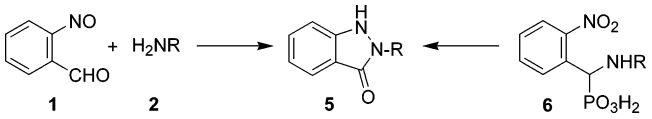


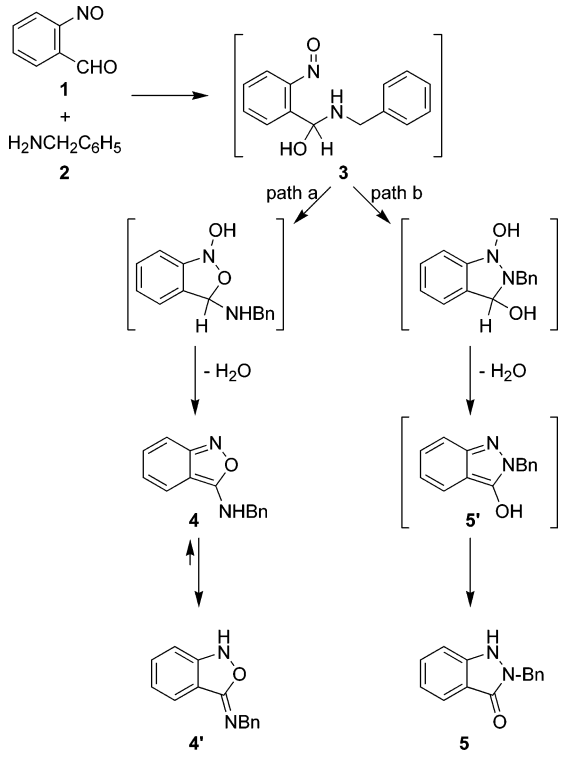
Claims, by two groups, to have prepared 2,1-benzisoxazole derivatives are corrected to show that the products are indazalones (**5**). In addition, a simple preparation of 3-oxy-substituted 2*H*-indazole, by an unrecognized method in the literature, is reported.

In relation to another project, we needed to prepare *o*-nitrosobenzaldehyde (**1**) and thus became aware of the relatively recent report of Chen and Burka[1] which, in turn, led us to the work of Boduszek, Halama, and Zon.[2] The Chen group claimed that *o*-nitrosobenzaldehyde (**1**) reacts with benzylamine (**2**) in $CHCl_3$ at room temperature to yield 3-benzylamino-2,1-benzisoxazole (anthranil **4** or its tautomer **4′**) and proposed path a in Scheme 1 to explain their assignment.

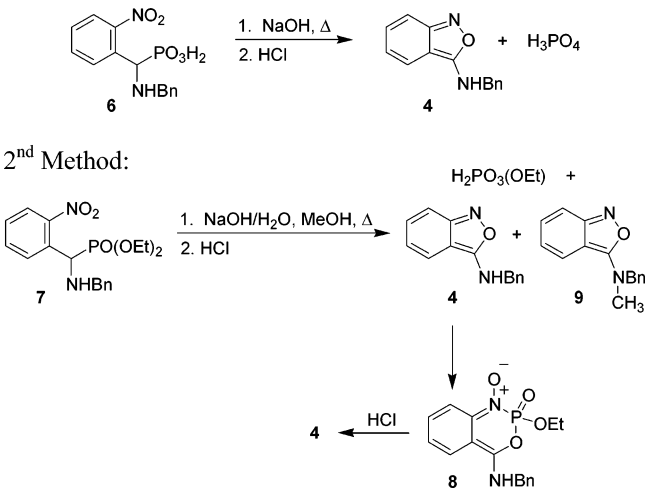
In support of their claim, these researchers cited the finding of the Boduszek group,[2] who reported the synthesis of "**4**" by two methods (Scheme 2), the second of which gives an additional product to which they speculatively assigned structure **9**. Given that secondary amines are more nucleophilic than secondary alcohols, we suspected that the product obtained by the Chen group[1] should be the indazalone derivative **5** (−NH attacking the −N=O, as depicted in Scheme 1/path b) rather than the reported 2,1-benzisoxazole derivative **4** or **4′** (−OH attacking the −N=O).

We therefore repeated the work of both groups[1,2] with regard to their common claim of having synthesized 3-benzylamino-2,1-benzisoxazole (**4**, **4′**). It is established below that indeed the methods used by either group lead to 2-*N*-benzylindazalone (**5**; Scheme 1). The structure of 2-*N*-benzylindazalone, obtained by the Chen or the Boduszek methods, was confirmed by comparison (IR, ^{1}H NMR, ^{13}C NMR) with a sample prepared by the method of Diez-Barra and co-workers[3] (Scheme 3).

SCHEME 1



SCHEME 2



Interestingly, the neat IR of **5** shows extended hydrogen bonding (3100−2500 cm^{-1}) and a rather low frequency, though strong, carbonyl absorption (1619 cm^{-1}; conjugation). Finally, we confirmed the structure of **5** (prepared by the Chen method)[1] by X-ray crystallography. The X-ray crystallographic structure in Figure 1 shows

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(1) Chen, L.-J.; Burka, L. T. *Tetrahedron Lett.* **1998**, *39*, 5351−5354.

(2) Boduszek, B.; Halama, A.; Zón, J. *Tetrahedron* **1997**, 53, 11399−11410. This reference includes more examples of alledged 2,1-benzisoxazoles prepared by the methods cited here in Scheme 2.

(3) Aran, V. J.; Diez-Barra, E.; de la Hoz, A.; Sanchez-Verdu, P. *Tetrahedron* **1997**, *45*, 129−136. Although there are other methods in the literature for the preparation of **5**, we chose this method because of its simplicity and the ^{13}C NMR data of the desired product.

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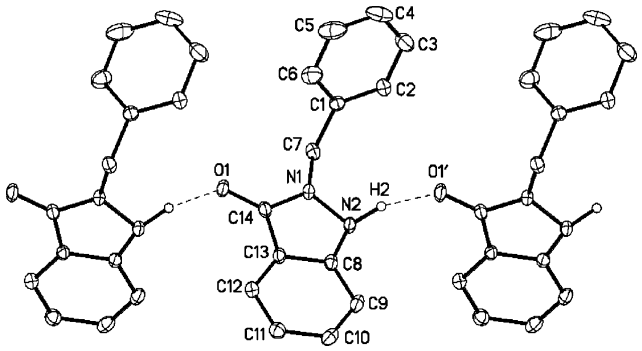
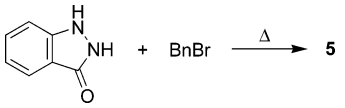
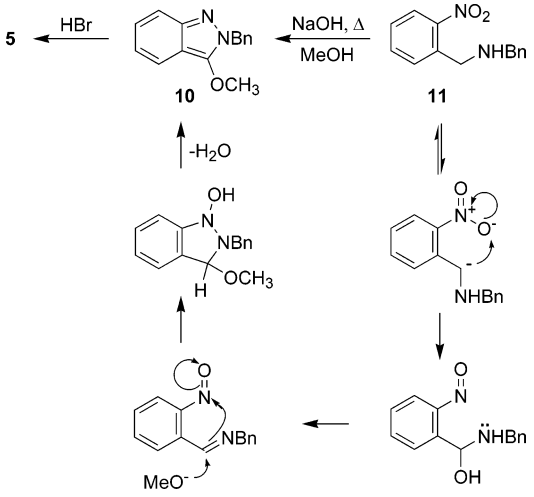


FIGURE 1. X-ray crystallographic structure of **5**.

SCHEME 3



SCHEME 4



clearly the extended H-bonding observed in the IR of **5** (note: the numbering of the X-ray structure is not related to the proper name of this compound).

Having established **5** as the true structure of "**4**, **4′**", we turned our attention to the additional product "**9**" (Scheme 2) obtained by the Boduszek group.[2] We predicted and verified that "**9**" is actually 3-methoxy-2-benzyl-2*H*-indazole (**10**). The Boduszek group[2] attributed the ^{1}H NMR methyl signal at δ 4.21 to the NCH_3 protons of "**9**", whereas it is more befitting of a methoxy group. Indeed, the ^{13}C NMR of the sample we prepared according to the prescribed procedure[2] showed two sp^3 hybridized carbons at δ 52.4 and 60.7, which is consistent with a methoxy carbon and an *N*-methylene benzylic carbon, respectively, with nitrogen being part of the 2*H*-indazole heteroring. Moreover, brief heating of **10** with 48% aqueous HBr converted it into **5** in 95% yield (Scheme 4).

By analogy with our earlier unpublished results with *N*-substituted *o*-nitrobenzylamines,[4] we envisaged that heating 2-nitro(*N*-benzyl)benzylamine (**11**)[5] with 5% methanolic KOH should give **10**. Indeed, this reaction proceeded smoothly to afford **10** in 61% yield. While a carbanion mechanism is proposed in Scheme 4, a radical-based alternative can be envisaged as well.[6] The generality of this simple and unrecognized method for the preparation of 3-oxy-substituted 2*H*-indazoles is being investigated further.[7] In Scheme 1, we propose how **5** is formed from **1** plus **2** (path b), and in Scheme 5, we suggest what we believe are likely mechanistic pathways to explain the conversion of **7**[2] to **5** and **10**. This postulated mechanism applies also to the conversion of **6** (Scheme 2) to **5**.

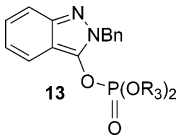
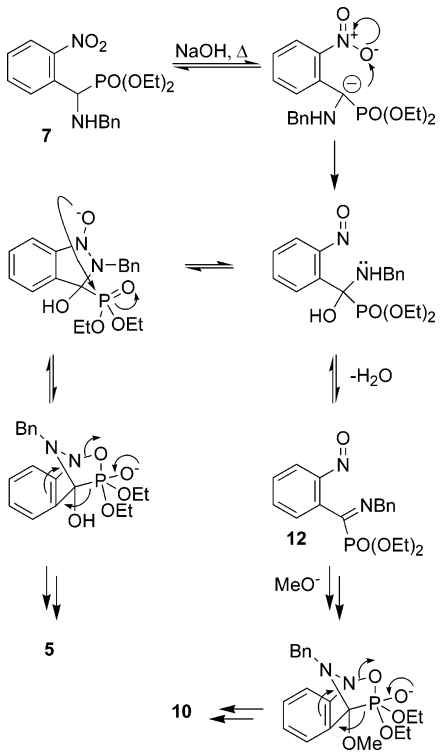


FIGURE 2.

SCHEME 5



The fact that **10** is formed in low yield (the Boduszek group[2] reported that "**9**" "never exceeding 20% even when the reaction was carried out in pure methanol") suggests that it could arise from a minor intermediate such as **12** (Scheme 5). Finally, it is evident that structure "**8**" (Scheme 2, 2nd method) assigned to the product of the reaction of "**4**" with monoethyl phosphonic acid (C_2H_5-OPO_3H_2) is structure **13** (Figure 2). The cited spectral data[2] and the ease of its cleavage to **5** are consistent with this structural assignment.

(4) Haddadin, M. J.; Nazer, M. Z.; Olmstead, M. M.; Kurth, M. J. Unpublished results.

(5) Ishikawa, F.; Watanabe, Y.; Saegusa, J. *Chem. Pharm. Bull.* **1980**, *28*, 1357−1364.

(6) Bjϕrsvik, H,-R.; González, R. R.; Liguori, L. *J. Org. Chem.* **2004**, *69*, 7720−7727.

(7) For a comprehensive review of the chemistry of indazoles, see: Stadlbauer, W. Product class 2: 1H- and 2H-indazoles. *Sci. Synth.* **2002**, *12*, 227−324.

It is evident that we (and others, though unknowingly[1,2]) demonstrate here a novel method for preparing 2-substituted indazalones. In addition, this method constitutes an easy method for constructing a N−N single bond.

Experimental Section

We confirm the experimental, physical, and spectral data of the isolated intermediates and products reported by both groups[1,2] leading to 2-benzylindazalone (**5**). *o*-Nitrosobenzaldehyde was prepared by the Bamberger method,[8] using O_2-degassed methanol as solvent and sunlight, followed by evaporation of the solvent and chromatography with Al_2O_3, *n*-hexane, and *n*-hexane/5% ethyl acetate. *o*-Nitro(*N*-benzyl)benzylamine (**11**) was prepared by either the literature method[5] or the following procedure: *o*-nitrobenzyl bromide (1,4 g, 6.5 mmol) was alkylated at room temperature with benzylamine (1.5 g, 14 mmol) in THF (10 mL) to give a white salt that was removed by filtration, the filtrate was evaporated, and the residue was chromatographed (neutral Al_2O_3, 50 g; elution with *n*-hexane/3% and 5% ethyl acetate) to give **11** (0.5 g, 32% yield).

2-Benzylindazalone (5): The procedure described by Chen and Burka[1] for the reaction of *o*-nitrosobenzaldehyde (**1**) and benzylamine (**2**) gave **5**, not the claimed 3-(*N*-benzylamino)-2,1-benzisoxazole **4** (or its tautomer **4′**; see Scheme 1).

3-Methoxy-2-benzyl-2*H*-indazole (10): *o*-Nitro(*N*-benzyl)-benzylamine (**11**, 0.5 g, 2.1 mmol) was dissolved in 5% methanolic KOH (50 mL). The solution was refluxed for 5 h. TLC showed almost complete conversion to the product. Methanol was evaporated, water was added, and the turbid solution was extracted with DCM (three 20-mL portions). The DCM extract was washed with 1 N HCl and washed again with water. The dried solution was evaporated to yield a yellow-colored oil that was purified by column chromatography (silica gel, 25 g; elution with *n*-hexane/5% ethyl acetate, 200 mL, 10%, 100 mL, 15%, 200 mL). Pale yellow oil, 0.3 g, 61%. The elemental analyses are reported.[2] The reported ^{1}H NMR and that measured by this work are identical. IR (neat) 1624 (s), 1526 (vs), 1510 (s), 1406 (s), 1385 (vs), 1113 (vs), 737 (s), 701 (s) cm^{-1}. ^{13}C NMR ($CDCl_3$) δ 52.14 (OCH_3), 60.53 ($NCH_2C_6H_5$), 107.00, 117.89, 119.58, 119.80, 126.26, 127.71, 127.93, 128.80, 136.48, 146.72, 147.48.

Conversion of 10 to the 2-Benzylindazalone 5: Compound **10** (11 mg, 0.05 mmol) was heated with aqueous 48% HBr (2 mL), with stirring for 1 min, and the cooled solution was diluted with water (10 mL). A white solid appeared and was collected, washed with water, and dried (9.8 mg, 95% yield). This compound was identical in all respects with **5**.

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Supporting Information Available: X-ray crystal structures for **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048153I

(8) Bamberger, E. *Chem. Ber.* **1918**, *51*, 606−12.