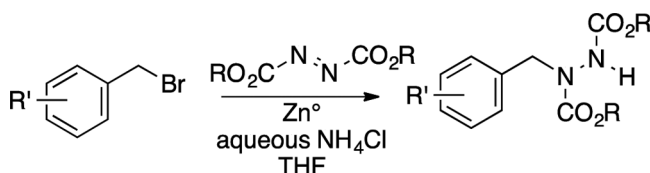


## CONVENIENT SYNTHESIS OF MONOBENZYLATED HYDRAZIDES VIA AQUEOUS ZINC-MEDIATED ADDITION REACTIONS

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### GRAPHICAL ABSTRACT



*R'* = alkyl, halogen, OCH<sub>3</sub>, CO<sub>2</sub>CH<sub>3</sub>      68-99% yields  
*R* = Et, *i*Pr, Bn, *tert*-Bu

**Abstract** Addition of substituted benzyl bromides to dialkyl azodicarboxylates under aqueous zinc-mediated addition conditions occurs readily to afford monobenzylated hydrazides in good to excellent yields. The reaction is tolerant of a variety of substituents on the benzyl bromide ring. Several dialkyl azodicarboxylates were successfully tested under the reaction conditions. The limitations of the reaction are also addressed.

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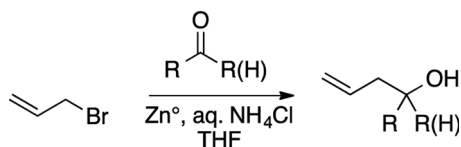
**Keywords** Aqueous; azodicarboxylate; hydrazide; zinc

## INTRODUCTION

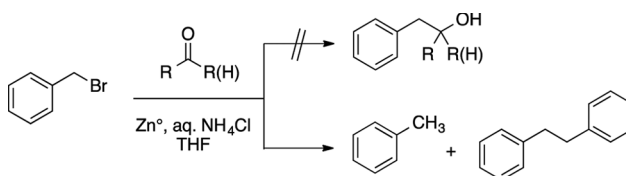
The aqueous zinc-mediated addition reaction of allyl halides to appropriate electrophiles (e.g., aldehydes, ketones, activated imines, nitroalkenes) has proven to be a convenient and powerful method in organic synthesis (Scheme 1).<sup>[1]</sup> Conducting such reactions under aqueous conditions rather than the typical anhydrous conditions required by most organometallic reactions has the obvious advantage of simplifying reaction setup (i.e., no prior drying of reagents, solvents, and reaction glassware is necessary) but also requires less organic solvent, thereby generating less chemical waste.<sup>[1]</sup> Although first discovered in 1978, advances in these metal-mediated aqueous

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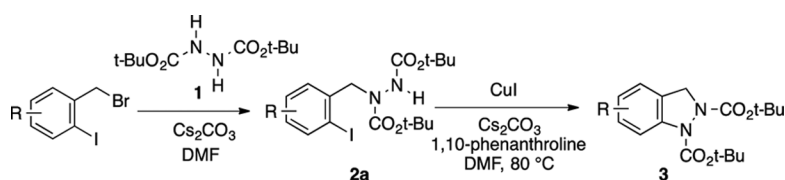
**Scheme 1.** General aqueous aqueous  $Zn^0$ -mediated addition reactions of allyl bromide with aldehydes and ketones.



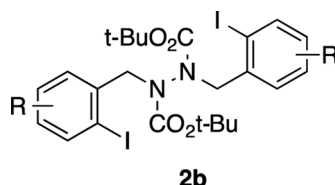
**Scheme 2.** Typical result from aqueous  $Zn^0$ -mediated addition reactions of benzyl bromide with aldehydes and ketones.

reactions continue even today.<sup>[1,2]</sup> Curiously, however, while allyl halides react readily under these conditions, benzyl halides are poor substrates, preferring to undergo net protonation and or Wurtz-type coupling rather than addition to electrophiles (Scheme 2).<sup>[3]</sup> A few recent advances have been made in the utilization of benzyl halides in such reactions, but these require the addition of expensive and/or toxic cocatalysts to promote reactivity.<sup>[3a,4]</sup>

Our recently reported studies on the synthesis of 2,3-dihydro-1*H*-indazoles (**3**) required the selective formation of monobenzylated hydrazides **2a** (Scheme 3).<sup>[5]</sup> We were frustrated by the tendency of di-*tert*-butyl hydrazodiformate (**1**) to form bisalkylated hydrazides **2b** (Fig. 1) rather than the desired monoalkylated hydrazides



**Scheme 3.** Synthetic route for 2,3-dihydro-1*H*-indazoles (**3**).



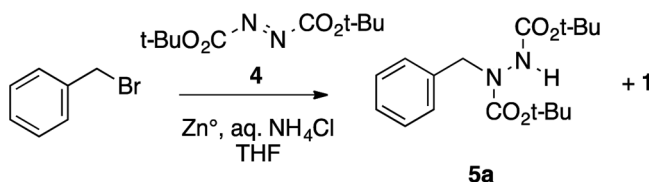
**Figure 1.** Structure of undesired bisalkylated hydrazides.

**2a** even though we utilized reaction conditions previously optimized by Rasmussen for its monoalkylation.<sup>[6]</sup> Others have struggled with similar problems of competing overalkylation in the reactions of hydrazines and their hydrazide derivatives.<sup>[6,7]</sup> Preformation of the hydrazide monoanion of **1** prior to the S<sub>N</sub>2 step has been suggested to favor monoalkylation over bisalkylation,<sup>[7b,8]</sup> but this solution is apparently not global.<sup>[8d]</sup> Given the importance of monoalkylated hydrazides in organic synthesis,<sup>[6,7,9]</sup> it is not surprising that the pursuit of methods to synthesize these compounds is still under active investigation.<sup>[6-10]</sup>

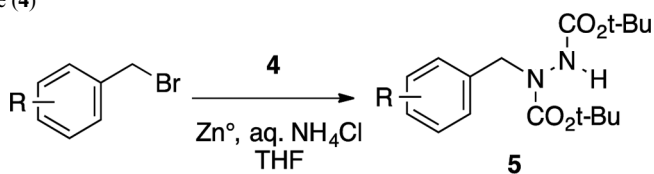
A few examples of the synthesis of monobenzylated hydrazides via the addition of benzyl organometallics to dialkyl azodicarboxylates have been reported.<sup>[11]</sup> However, these studies were all conducted under typical anhydrous conditions. Furthermore, we could find no studies that investigated the scope of the reaction. It would be beneficial if these reactions were amenable to being conducted under the aqueous zinc-mediated conditions discussed above. Upon investigation, we are delighted to report that benzyl substrates can be successfully added to dialkyl azodicarboxylates under aqueous zinc-mediated conditions to afford the desired monobenzylated hydrazides in good to excellent yields despite their previously reported reluctance to react under similar conditions.<sup>[3]</sup>

## DISCUSSION

To initially test for reactivity, 1 mmol of benzyl bromide in 2 mL of tetrahydrofuran (THF) was added to a stirring mixture of 1 equivalent each of Zn metal and di-*tert*-butyl azodicarboxylate (**4**) in 1 mL of saturated aqueous NH<sub>4</sub>Cl (Scheme 4). After 3 h the reaction mixture was filtered to remove zinc salts that had formed. Analysis of the crude reaction mixture by <sup>1</sup>H NMR spectroscopy revealed an approximate 50/50 mixture of monoalkylated hydrazide **5a** and starting benzyl bromide. In addition to remaining **4** there was also hydrazide **1**, apparently formed from direct reduction of **4** by the zinc metal. A control reaction demonstrated that **4** does indeed react quantitatively with zinc metal under the reaction conditions in the absence of benzyl bromide to form **1**. To counteract this competing reaction, the amounts of **4** and zinc were increased. A 1:2:2 reaction mixture of benzyl bromide, **4**, and zinc under identical reaction conditions afforded a 3:1 mixture of **5a** to benzyl bromide, suggesting that most, but not all, of the starting benzyl bromide was able to compete with **4** in its reaction with zinc. Finally, increasing the amount of zinc to 3 equivalents (overall 1:2:3 ratio of benzyl bromide–**4**–zinc) resulted in complete consumption of starting material and addition product **5a** was afforded in 91% isolated yield (see Table 1). Given this success, a series of benzyl bromides was subjected to identical reaction conditions (method A). The results are compiled in Table 1. In general, good



**Scheme 4.** Reaction of benzyl bromide with **4** and Zn<sup>0</sup> under aqueous Zn-mediated conditions.

**Table 1.** Aqueous Zn<sup>0</sup>-mediated addition reaction of substituted benzyl bromides to di-*tert*-butyl azodicarboxylate (**4**)

Entry	Substrate	Product	Yield (%)	
			Method A <sup>a</sup>	Method B <sup>b</sup>
1		<b>5a</b>	91	92
2		<b>5b</b>	88	
3		<b>5c</b>	74	
4		<b>5d</b>	86	
5		<b>5e</b>	86	
6		<b>5f</b>	79	
7		<b>5g</b>	99	
8		<b>5h</b>		74
9		<b>5i</b>	ND <sup>c</sup>	
10		<b>5j</b>	81	74

(Continued)

Table 1. Continued

Entry	Substrate	Product	Yield, %	
			Method A <sup>a</sup>	Method B <sup>b</sup>
11		<b>5k</b>	77	79
12		<b>5l</b>	ND <sup>c,d</sup>	
13		<b>5m</b>	28 <sup>e</sup>	

<sup>a</sup>1:2:3 mixture of benzyl bromide-**4**-Zn°.

<sup>b</sup>2:1:2 mixture of benzyl bromide-**4**-Zn°.

<sup>c</sup>None detected.

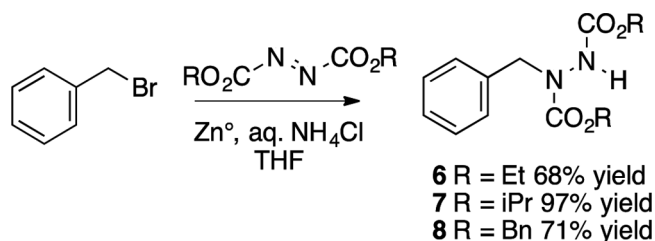
<sup>d</sup>Only dimerized product was observed.

<sup>e</sup>Conducted in aqueous K<sub>2</sub>HPO<sub>4</sub> rather than NH<sub>4</sub>Cl.

to excellent yields of the anticipated monobenzylated hydrazides were obtained. The reaction was tolerant of the presence of a variety of substituents on the aromatic ring including alkyl groups (entries 2 and 3), various halogens (entries 4–6), the methoxy group (entry 7), and the carbomethoxy group (entry 8). The presence of a nitro group (entry 9), however, suppressed the reaction. In addition to the starting material, several minor products were observed as well as hydrazide **1**, but no evidence for formation of any appreciable amount of product **5i** was observed from the <sup>1</sup>H NMR spectrum of the crude reaction mixture or by thin-layer chromatographic (TLC) analysis.

Although reaction was successful with 3-carbomethoxybenzyl bromide (entry 8) employing method A, we found it difficult to cleanly separate the hydrazide product **5h** from by-product **1** using column chromatography. Therefore, an alternative method was developed to limit the formation of **1**. According to this method (method B) an excess of substituted benzyl bromide (2 mmol) was added to a single equivalent of **4** in the presence of Zn (2 mmol). The lesser amount of hydrazide **1** by-product formed by this method allowed for much easier purification of the desired addition products. We tested this method on a few other substrates and observed comparable results to those using method A (entries 1, 10, and 11).

The secondary bromide (1-bromoethyl)benzene also underwent reaction successfully (entry 11) to afford **5k**. The major by-product observed was the dimeric compound 2,3-diphenylbutane. In contrast, bromodiphenylmethane (entry 12) failed to yield any of the desired hydrazide product **5l**. The only product observed resulted from dimerization of the bromide to form 1,1,2,2-tetraphenylethane. We attempted



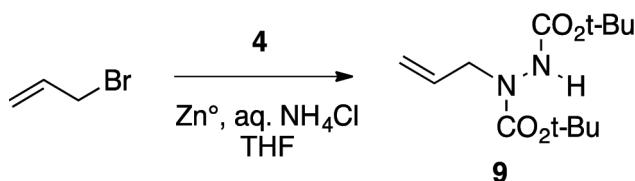
**Scheme 5.** Aqueous  $\text{Zn}^\circ$ -mediated addition of benzyl bromide to other dialkyl azodicarboxylates.

to minimize the dimerization process by slow addition (via syringe pump) of a THF solution of the bromide to a stirring mixture of **4** and  $\text{Zn}^\circ$  in saturated aqueous  $\text{NH}_4\text{Cl}$  without success. Similarly, slow addition of a premixed THF solution of the bromide and **4** to the  $\text{Zn}^\circ$  did not afford the addition product. Perhaps because of its large *tert*-butyl groups, **4** is simply too sterically hindered of an electrophile to accept such a sterically hindered intermediate generated from this particular benzyl bromide.

3-Bromomethylpyridine (used as the HBr salt) was unreactive under the reaction conditions of method A (96% of starting **4** was accounted for as a 6:1 mixture of **1** to unreacted **4**). We suspected that the acidic aqueous ammonium chloride conditions were responsible. We tried conducting the reaction under basic conditions previously developed by Bieber et al. (1.5 g  $\text{K}_2\text{PO}_4$ /1.5 mL water/THF)<sup>[3a]</sup> but observed only trace amounts of product **5m**. Addition of a catalytic amount of  $\text{AgNO}_3$  to enhance reactivity (also according to the Bieber procedure)<sup>[3a]</sup> resulted in complete consumption of the pyridine substrate and isolation of **5m** in a poor 28% yield. The major by-product (by  $^1\text{H}$  NMR analysis of the crude reaction mixture) appeared to be 3-methylpyridine, resulting from protonation of the radical anion.

In addition to azodicarboxylate **4**, the reaction was also successful (method A, Scheme 5) using the electrophiles diethyl azodicarboxylate (to afford **6**, 68% yield), diisopropyl azodicarboxylate (**7**, 97% yield), and dibenzyl azodicarboxylate (**8**, 71% yield). All of these reactions were significantly faster (<30 min for loss of the characteristic yellow color of the azodicarboxylate) than the corresponding reactions with **4**, conceivably due to the lesser amount of steric hindrance from their respective  $\text{CO}_2\text{R}$  groups.

Finally, allyl bromide was also subjected to the reaction conditions (method B, Scheme 6) to afford addition product **9** in 56% yield. Although only moderate, this yield compares favorably to the reported yield (50%) obtained by direct allylation of **1** where bisalkylation effectively competes.<sup>[7d]</sup>



**Scheme 6.** Aqueous  $\text{Zn}^\circ$ -mediated addition of allyl bromide to **4**.

## EXPERIMENTAL

Column chromatography was conducted on silica gel (234–400 mesh) using compound-appropriate mixtures of hexanes and EtOAc as eluent. Thin-layer chromatography was performed on precoated silica-gel plates (250 mm) and visualized by ultraviolet light and/or by visualization with I<sub>2</sub> vapor. The I<sub>2</sub> vapor was especially helpful for visualizing the reduced unsubstituted hydrazides. <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained on a 400-MHz NMR spectrometer unless otherwise specified, and were generally collected at 60 °C to simplify the spectra which are terribly complicated at room temperature due to conformational restrictions. Chemical shifts are reported in units of parts per million downfield from tetramethylsilane (TMS). Elemental analyses were performed by a commercial laboratory. High-resolution mass spectral (HRMS) analysis was performed via gas chromatography (GC)–MS (TOF EI). Diethyl azodicarboxylate (DEAD) was synthesized via N-bromosuccinimide (NBS) oxidation of the corresponding commercially available hydrazide and purified by column chromatography immediately prior to use.<sup>[12]</sup> All other chemicals and solvents were obtained from commercial sources and used without further purification.

### General Procedure: Method A

To 0.195 g (3 mmol) of Zn metal in 1 mL saturated aqueous NH<sub>4</sub>Cl solution was added 0.46 g (2 mmol) of **4**. Stirring was begun and a solution of the appropriate benzyl bromide (1 mmol) in 2 mL of THF was added via pipette. The reaction vessel was capped and the mixture allowed to stir until the yellow color of **4** was discharged (generally ~3 h). The reaction mixture was filtered through a plug of glass wool into a centrifuge tube. The organic layer was removed. The aqueous layer was washed 2×2 mL of THF. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Column chromatography on SiO<sub>2</sub> using appropriate mixtures of ethyl acetate and hexanes provided the desired compounds.

### General Procedure: Method B

To 0.13 g (2 mmol) of Zn metal in 1 mL saturated aqueous NH<sub>4</sub>Cl solution was added 0.23 g (1 mmol) of **4**. Stirring was begun and a solution of the appropriate benzyl bromide (2 mmol) in 2 mL of THF was added via pipette. The reaction vessel was capped and the mixture allowed to stir until the yellow color of **4** was discharged (generally ~3 h). The reaction mixture was filtered through a plug of glass wool into a centrifuge tube. The organic layer was removed. The aqueous layer was washed 2×2 mL of THF. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Column chromatography on SiO<sub>2</sub> using appropriate mixtures of ethyl acetate and hexanes provided the desired compounds.

### ***N***-Benzyl-*N'*-[(*tert*-butoxy)carbonyl] (*tert*-butoxy)carbohydrazide (**5a**)<sup>[6,11b–d]</sup>

According to method A, from 0.171 g (1 mmol) of benzyl bromide was obtained 0.291 g (91% yield) of **5a** as a white solid: mp 101.8–103.0 °C (lit.<sup>[11b]</sup> 102–104 °C); <sup>1</sup>H

NMR (CDCl<sub>3</sub>, 60 °C) δ 7.29–7.25 (m, 5H), 6.33 (br s, 1H), 4.60 (br s, 2H), 1.47 (s, 9H), 1.42 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 60 °C) δ 155.3, 155.1, 137.3, 128.5(2C), 127.5, 81.3, 81.0, 53.7(br), 28.3, 28.2.

## FUNDING

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## SUPPORTING INFORMATION

Full experimental details and <sup>1</sup>H and <sup>13</sup>C NMR spectra for all synthesized compounds can be found via the Supplementary Content section of this article's Web page.

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