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A Hydrazine Insertion Route to *N*′-Alkyl Benzohydrazides by an Unexpected Carbon−Carbon Bond Cleavage

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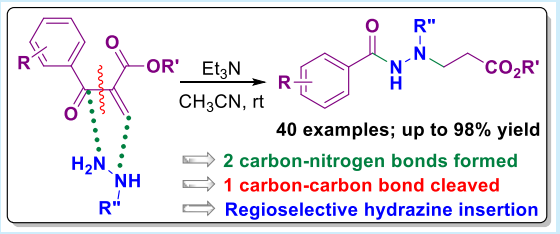
Supporting Information

ABSTRACT: A serendipitous carbon−carbon bond cleavage in the reaction of benzoyl acrylates, derived from Morita−Baylis−Hillman adducts, with hydrazines delivered new *N*′,*N*′-disubstituted benzohydrazides. The reaction features a regioselective formation of two carbon−nitrogen bonds and works well with a range of acrylates and hydrazines. A brief mechanistic investigation alluded to a cyclic hemiaminal as a plausible intermediate.



The Morita−Baylis−Hillman (MBH) reaction[1,2] delivers adducts which are multifunctional and can be manipulated in myriad ways.[3] One such transformation is the oxidation of the allylic alcohol,[4] which affords the corresponding "MBH ketone". These 1,1-disubstituted olefins flanked by two electron-withdrawing groups have attracted considerable attention owing to their reactivity as Michael acceptors and their ability to participate in Diels−Alder reactions as a dienophile as well as heterodiene. Transformations of MBH ketones have been explored by either generating them *in situ*[5,6] or using the isolated compound.[7] The former has been achieved in two different ways, *viz* (i) IBX mediated oxidation of MBH adducts[5] and (ii) Knoevenagel condensation of 1,3-dicarbonyls with formaldehyde,[6] followed by trapping the conjugated olefin in Michael or Diels−Alder fashion. On the other hand, numerous reports can also be found on transformations of MBH ketones that have been synthesized and isolated, albeit not always by oxidation of an MBH adduct.[7] A majority of them pertain to the Diels−Alder reaction, including an asymmetric version and an application in natural product synthesis.[7a−d] Other noteworthy instances include a [3 + 2] cycloaddition to generate isoxazolines,[7e] synthesis of vicinal tricarbonyl compounds by ozonolysis,[7f] and access to functionalized 1,4-dicarbonyl compounds by a Stetter reaction.[7g]

On the other hand, substituted hydrazides are known to exhibit interesting biological activity, reflected by their role in peptidomimetics and other commercial applications.[8−10] The most interesting are the *N*,*N*′-diacyl hydrazines, chief among them *N*′-*tert*-butyl substituted benzohydrazides, that have attracted tremendous interest as growth regulators of *Lepidopteran* insects.[11] The earliest such report was of RH5849,[11a,b] followed by Tebufenozide—the first commercial nonsteroidal ecdysone agonist,[11c] and several structural analogs.[11d−g] Also, *N*′-alkyl hydrazide analogs such as isocarboxazid and iproniazid are classical monoamine oxidase inhibitors (MAOIs) that have been used for the treatment of anxiety disorders.[12] Furthermore, a recent report found both *N*′-alkyl and *N*′-acyl substituted 3-furoic hydrazides to be promising candidates for antischistosomal activity.[13] In addition to their medicinal value, substituted hydrazides have also been utilized in the synthesis of 1*H*-indazolones,[14] 2-imino 1,3,4-oxadiazolines,[15] and *N*-acylhydrazones that exhibit promising bioactivity.[16,17] Hence, research on the synthesis of substituted hydrazines and hydrazides has witnessed continued activity;[12,18] new analogs and strategies for their synthesis would be of interest to the chemical and pharmaceutical research community.

In the quest of exploring the reactivity of MBH ketones, we serendipitously observed a reaction that afforded new *N*′-alkyl substituted benzohydrazides. We carried out deeper investigations into the transformation, and the findings of the study are presented herein.

Our group has been evaluating controlled base-mediated Michael additions of heteroatomic nucleophiles to the highly reactive MBH ketone. Simultaneously, we were also looking to connect its two electrophilic ends to dinucleophiles, in typical fashion involving concomitant Michael addition−condensation, to construct five-membered heterocycles. In one such experiment in the midst of these studies, when we treated MBH ketone **1a** with phenylhydrazine (**2a**) in the presence of Et_3N in THF at room temperature, the major product formed turned out to be neither a pyrazoline nor the aromatized pyrazole expected on the above lines; instead, we deciphered it to be the *N*′,*N*′-disubstituted benzohydrazide **3a** (Scheme 1) on the basis of two distinct methylenes observed in the ^1H NMR spectrum, supported by a ^{13}C NMR scan that indicated the presence of an amide group; additionally, mass spectrometric analysis revealed an atom economic transformation. X-ray crystal analysis of an analog helped us

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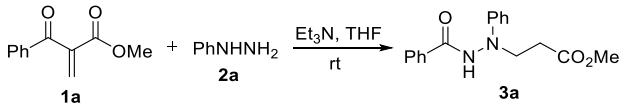
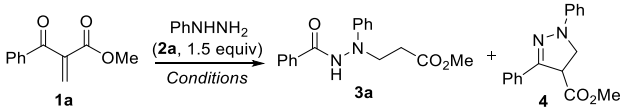
Scheme 1. Reaction of 1a with 2a to Generate a Benzohydrazide



confirm both the structure and the regiochemistry of the phenylhydrazine insertion (Scheme 2, **3b**). Thus, it could be inferred that N^2 of **2a** translated to the amide nitrogen, whereas N^1 was linked to the alkyl chain in the product **3a**. To sum up the transformation, two new carbon−nitrogen bonds are formed in the interaction of phenylhydrazine with the MBH ketone, whereas the accompanying carbon−carbon bond cleavage led to the formation of the acyclic benzohydrazide. It is worth noting that the bond formed in the MBH reaction at the outset is eventually cleaved in the process. To our knowledge, this is the first instance of such a carbon−carbon bond cleavage occurring in a substrate derived from an MBH reaction. Further, despite the substantial literature on the synthesis of hydrazines, a one-step access to *N*-acyl-*N*′-alkyl analogs by insertion of a hydrazine does not appear to have precedent. Lastly, considering the challenges pertaining to N^1/N^2 selectivity in hydrazine alkylations,[19,20] a prominent feature of the present transformation is the regioselectivity achieved in the insertion of phenylhydrazine using a mild organic base.

These interesting features urged us to undertake a detailed study of the transformation, commencing with the optimization of the conditions for the reaction of **1a** with **2a** (Table 1). The requirement of a base for the formation of **3a** was revealed by a reaction in its absence, which resulted exclusively in the pyrazoline **4** instead of **3a** (entry 1). A short survey of solvents was then carried out for the reaction in the presence of Et_3N, and it was found that CH_3CN was the best (entries 2−5). Lowering the stoichiometry of the base or the hydrazine did not greatly affect the efficiency of the reaction outcome (entries 6−10); 10 mol % of Et_3N sufficed to deliver a similar yield of **3a** over the same duration (entry 9). Next, a study of bases was undertaken; organic bases generally produced a mixture of **3a** and **4** (entries 11−14); interestingly, the use of pyridine as the base as well as solvent afforded pyrazoline **4** exclusively (entry 15). Use of NaH and ^{n}BuLi as bases proved futile (entries 16 and 17), whereas the use of Cs_2CO_3 provided the only instance of formation of the *N*-phenyl regioisomer **3a**′, alongside the desired **3a** (entry 18).[21]

Table 1. Optimization of Reaction Conditions[a]



				yield [%][b]	
entry	base [equiv]	solvent	time [h]	**3a**	**4**
1	–	THF	24	0	50
2	NEt_3 [2.5]	THF	17	65	10
3	NEt_3 [2.5]	CH_3CN	12	88	trace
4	NEt_3 [2.5]	dioxane	12	76	trace
5	NEt_3 [2.5]	toluene	12	80	trace
6	NEt_3 [1.5]	CH_3CN	15	83	trace
7	NEt_3 [1.0]	CH_3CN	15	82	trace
8	NEt_3 [0.5]	CH_3CN	15	83	trace
9	NEt_3 [0.1]	CH_3CN	15	79	trace
10[c]	NEt_3 [0.5]	CH_3CN	15	76	trace
11	pyrrolidine [0.5]	CH_3CN	15	71	15
12	imidazole [0.5]	CH_3CN	15	40	28
13	*N*-methyl imidazole [0.5]	CH_3CN	15	27	32
14	DMAP [0.5]	CH_3CN	15	63	15
15	pyridine[d]	pyridine	15	–	54
16	^{n}BuLi [1.2]	THF	24	–	–
17	NaH [1.2]	THF	1	–	–
18	Cs_2CO_3 [0.5]	CH_3CN	10	57[e]	trace

[a]Reactions were carried out on 0.5 mmol of **1a** using 500 μL of the solvent at rt. [b]Refers to isolated yield after column chromatographic purification. [c]1.2 equiv of **2a** was used. [d]Used as a solvent. [e]Refers to the yield of the mixture of **3a** and its regioisomer **3a**′.

We then sought to explore the scope of this new method of generating benzohydrazides by using various MBH ketones in reactions with the aromatic hydrazines **2a** and **2b** under the optimized conditions. The reaction worked well with substituents of differing electronic character on the aromatic ring of **1**. As shown in Scheme 2, halogen substituents at the *para*-position proved favorable in delivering the corresponding benzohydrazides with excellent efficiency. Reactions of MBH ketones bearing strong electron-donating (*p*-OMe) and electron-withdrawing (*p*-NO_2) substituents proceeded with comparable efficiency, highlighting the generality of the process. A fruitful outcome could also be achieved using a *meta*-substituted variant as well as a heteroaryl MBH ketone, resulting in substantial yields of the benzohydrazides **3h** and **3i**, respectively. Further, ethyl benzoacrylate analogs participated in similar fashion to their methyl counterparts and afforded the benzohydrazides **5a−i** in reasonable to high yields. Lastly, the reaction also worked well using a different hydrazine—the *p*-chlorophenyl analog **2b**. The efficiency of the reaction using **2b** also remained largely unaffected by the nature of the aromatic component in **1**; benzohydrazides **3j−m** and **5j−m** (methyl and ethyl ester derivatives, respectively) could thus be generated in satisfactory yields.[22]

To study the reaction using an aliphatic hydrazine, we chose the *tert*-butylhydrazine (**2c**) based on the huge impact of the *N*′-*tert*-butyl substituted hydrazides as insecticides. Gratifyingly, the reaction[22] proceeded well and a number of *N*′-*tert*-butyl substituted benzohydrazide analogs could be generated from various MBH ketones (Scheme 3). 4-Halo substituents proved favorable once again for obtaining good yields of the hydrazides. The use of the *meta*-chlorophenyl variant afforded a crystal of the corresponding benzohydrazide **3r**, X-ray analysis of which confirmed that the aliphatic hydrazine mirrored the regioselectivity of its aromatic counterparts. Overall, we were able to access several new *N*′-*tert*-butyl substituted benzohydrazides in moderate yields. Lastly it is worth mentioning that the reaction also proceeded well using simple hydrazine and is currently being studied in more detail for its scope.

After the scope of the reaction was examined, a mechanistic interpretation of the observations was probed. A plausible pathway for the reaction is illustrated in Scheme 4. At the outset, aza-Michael addition of phenylhydrazine (**2a**) to the MBH ketone **1a** leads to the intermediate **I**; intramolecular condensation could then be expected to afford pyrazoline **4** via the intermediacy of cyclic hemiaminal **II**. However, in the presence of Et_3N, **II** perhaps undergoes base catalyzed proton transfer accompanied by a carbon−carbon bond cleavage, leading to the formation of **3a**. Alternatively, a concerted acyl

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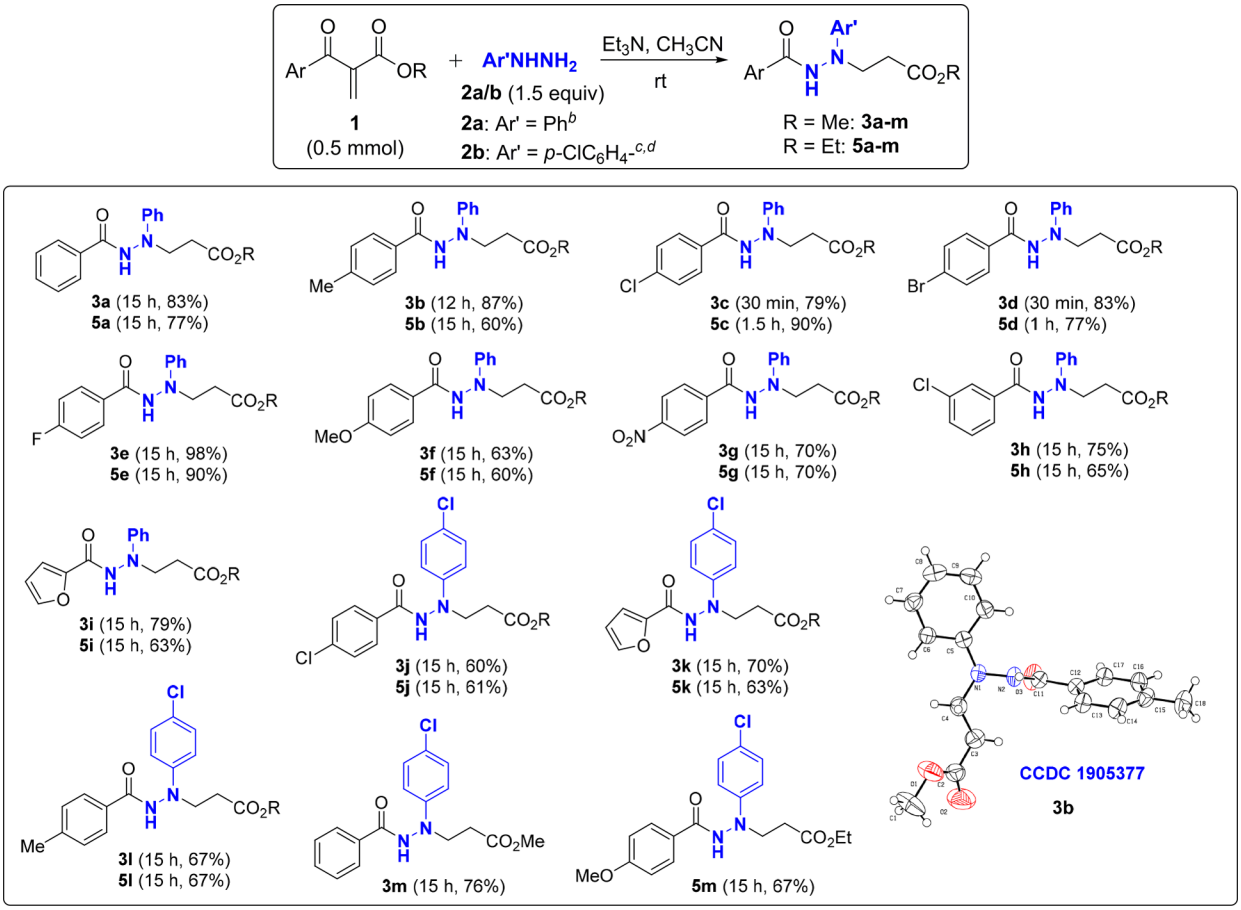
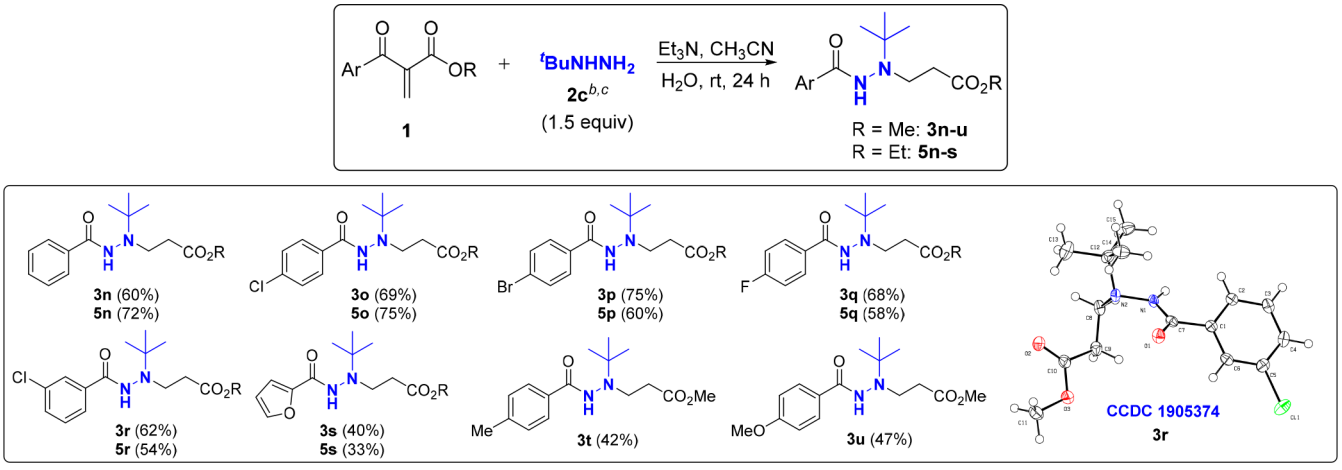
Scheme 2. Benzohydrazides from the Reaction of 1 with Aryl Hydrazines[a]



[a]Yields refer to isolated yields after column chromatographic purification. [b]Reactions were carried out using 0.5 equiv of Et_3N in 500 μL of CH_3CN. [c]**2b** was prepared and used as a hydrochloride. [d]Reactions were carried out using 3.5 equiv of Et_3N and 50 μL of H_2O in 500 μL of CH_3CN.

Scheme 3. Benzohydrazides from the Reaction of 1 with *tert*-Butylhydrazine (2c)[a]



[a]Yields refer to isolated yields after column chromatographic purification. [b]Used as a hydrochloride. [c]Reactions were carried out on 0.5 mmol of **1** using 3.5 equiv of Et_3N, 500 μL of CH_3CN, and 50 μL of H_2O.

transfer occurring on **I** to directly deliver **3a** may also be considered.[23] To gain insight into the pathway, we set up the reaction of **1a** with **2a** monitored by ^1H NMR spectroscopy.[24] After 15 min in the absence of Et_3N, the ^1H NMR spectrum of the crude reaction mixture showed complete consumption of **1a** and formation of pyrazoline **4** (signals at δ 4.07, 4.35, and 4.48 ppm); no characteristic peaks of **3a** were observed at this stage. In contrast, the ^1H NMR spectrum recorded 15 min after the addition of Et_3N showed the appearance of a singlet at δ 3.63 and two triplets at δ 2.77 and 3.97, indicating the

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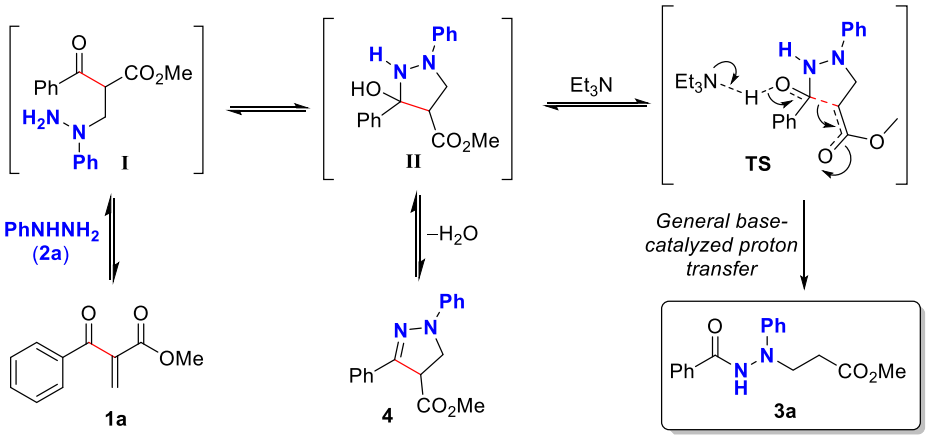
Scheme 4. Plausible Mechanistic Pathway for the Reaction of 1a with 2a Leading to the Formation of 3a



formation of **3a**. The intensity of the peaks corresponding to **3a** increased with time, accompanied by a gradual disappearance of the signals corresponding to pyrazoline **4**.[25] The study supports the pathway illustrated in Scheme 4, in which one may imagine the intermediate **II** to be in a dynamic equilibrium with both **4** and **3a**; the former has a dominant presence in the initial stages of the reaction, whereas the acyclic hydrazide manifests as the eventual major product after addition of the base. A control experiment was also performed to attempt the conversion of isolated pyrazoline **4** to **3a** using H_2O/Et_3N; however it did not prove successful, perhaps suggestive of the origin of hemiaminal **II** and the dynamic nature of the equilibrium in the parent reaction. The study also suggests that the reaction does not proceed through a concerted acyl transfer mechanism, but rather an addition–elimination sequence. It is worth noting that the loss of a carbon–carbon bond in the process prevails over the formation of a heterocycle with a propensity for aromatization.

In summary, new *N*′,*N*′-disubstituted benzohydrazides were synthesized by the reaction of MBH ketones with aryl/alkyl hydrazines in the presence of triethyl amine. The reaction features a regioselective insertion of the hydrazine into the benzoyl acrylate skeleton. A brief mechanistic study indicated the involvement of a cyclic hemiaminal intermediate that preferentially breaks down to the acyclic amide by a general base mediated proton transfer.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02657.

Experimental procedures, spectroscopic characterization data, and ^1H and ^{13}C NMR spectra of the synthesized compounds (PDF)

Accession Codes

CCDC 1905374 and 1905377 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(21) The regioisomeric ratio was 3:2 in favour of **3a**, as determined by ^{1}H NMR of the isolated product.

(22) An excess of the base, Et_3N, was used in these reactions to liberate the free hydrazine from its hydrochloride salt.

(23) The formation of traces of pyrazoline in the reactions ought not to be considered a confirmation of the pathway and intermediacy of the hemiaminal.

(24) In practice, five independent reactions were set up under identical conditions employing identical quantities and addition sequences. This was necessary to avoid a decrease in the concentration of Et_3N owing to repeated aliquots drawn from the reaction.

(25) See Supporting Information for illustration of ^{1}H NMR spectra of this study.

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