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Efficient Synthesis of 1,5-Disubstituted Carbohydrazones Using K_2CO_3 As a Carbonyl Donor

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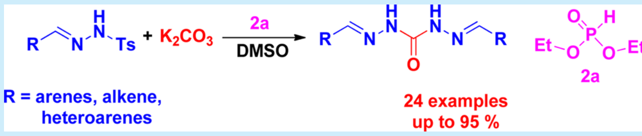
Supporting Information

ABSTRACT: A novel reaction that generates 1,5-disubstituted carbohydrazones via the carbonylation of tosylhydrazones has been developed. For the first time, the inexpensive, readily available, environmentally friendly, and nongaseous potassium carbonate is used as the carbonyl donor for the transformation. The reaction system exhibited tolerance with various functional groups and affords the desired products in good to excellent yields. This reaction is expected to be a powerful tool for the synthesis of carbohydrazone compounds.



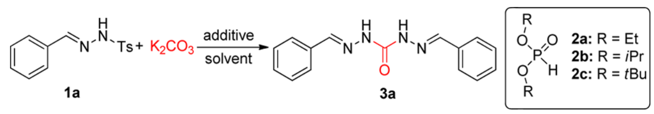
Ureylene-containing compounds have often been explored in the development of pharmaceuticals, agricultural pesticides, gasoline antioxidants, and corrosion inhibitors.[1] Carbohydrazones, in particular, exhibit diverse utility, including as antibacterial[2] and anticonvulsant[3] agents, highly efficient chemosensors,[4] and valuable synthetic intermediates.[5]

A number of methodologies for the synthesis of ureylene-containing compounds (carbohydrazones, ureas) have been reported. However, these strategies mainly employ phosgene and triphosgene,[6] CO,[7] and CO_2[8] as sources of the carbonyl moiety, despite their associated significant drawbacks. Phosgene is corrosive, CO is an explosive gas, and both of them are highly toxic. CO_2 is often used in large excess under high pressure, thus complicating the process. Recently, alternative carbonyl group donors have been developed, such as organic carbonates,[9] isocyanate,[10] formamides,[11] and carbonylimidazolium salts.[12] Nevertheless, some of these reagents originate from phosgene or require costly multistep syntheses. Therefore, it remains an important challenge to develop an inexpensive, readily available, and environmentally benign carbonyl donor.

Herein, we report the novel phosphite-mediated synthesis of 1,5-disubstituted carbohydrazones by the carbonylation of different tosylhydrazones using potassium carbonate as the carbonyl donor. These facile reactions were carried out in the absence of transition metals, and a wide variety of substituted carbohydrazones were obtained in good to excellent yields. Interestingly, potassium carbonate, one of the most common inorganic bases, was used as the carbonyl donor for the first time; the reagent is inexpensive, ecologically friendly, abundant, nonflammable, and nongaseous.

For the initial optimization of the reaction conditions, the carbonylation of tosylhydrazone **1a** was selected as a model reaction system. The results are listed in Table 1. The first attempted reactions, using K_2CO_3 as the carbonyl donor and dimethyl sulfoxide (DMSO) as the solvent (Table 1, entry 1), afforded no carbonylation product. Addition of phosphite **2a** to the reaction system led to the desired product 1,5-dibenzyl carbohydrazone (**3a**) in 82% yield (Table 1, entry 2). We probed additive stoichiometry on a small scale (entries 2−4) and found that 1.0 equiv of **2a** was optimal for the reaction, affording a 92% yield of product (entry 4). The use of other dialkyl phosphites as additives resulted in lower yields (entries 5 and 6); increasing alkyl group bulkiness decreased the product yield, indicating that the reaction may sensitive to steric effects from the dialkyl phosphites. A solvent evaluation revealed that DMSO was nearly the only suitable solvent for the reaction

Table 1. Optimization of Reaction Conditions[a]



entry	additive (mol %)	solvent	carbonyl donor	temp (°C)	yield of 3a (%)[b]
1	–	DMSO	K_2CO_3	60	NR
2	**2a** (150)	DMSO	K_2CO_3	60	82
3	**2a** (50)	DMSO	K_2CO_3	60	45
4	**2a** (100)	DMSO	K_2CO_3	60	92
5	**2b** (100)	DMSO	K_2CO_3	60	83
6	**2c** (100)	DMSO	K_2CO_3	60	45
7	**2a** (100)	DMF	K_2CO_3	60	11
8	**2a** (100)	dioxane	K_2CO_3	60	0[d]
9	**2a** (100)	EtOH	K_2CO_3	60	0[d]
10	**2a** (100)	toluene	K_2CO_3	60	0[d]
11	**2a** (100)	DMSO	Na_2CO_3	60	trace
12	**2a** (100)	DMSO	$KHCO_3$	60	trace
13	**2a** (100)	DMSO	K_2CO_3	80	31
14	**2a** (100)	DMSO	K_2CO_3	40	78
15[c]	**2a** (100)	DMSO	K_2CO_3	60	93

[a]Reaction conditions: **1a** (0.5 mmol), K_2CO_3 (0.75 mmol), solvent (2 mL), 10 h, 60 °C, in air. [b]Isolated yield. [c]99.995% K_2CO_3 was used. [d]The phosphorohydrazone **7** was obtained as the product.

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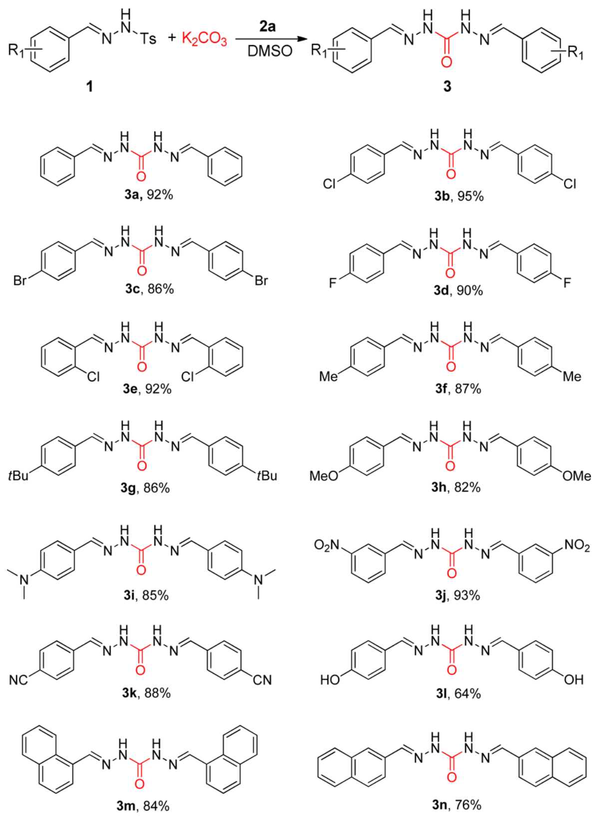
(entries 7−10). The use of other carbonates as the carbonyl donor, such as Na_2CO_3 and $KHCO_3$ (entries 11, 12), provided only trace amounts of the desired products. The optimal reaction temperature was 60 °C (entries 4, 13, and 14); at higher temperatures, larger quantities of byproducts were formed. To exclude the possibility that trace impurities were affecting the reaction, we performed a control experiment using ultrapure K_2CO_3 (99.995%) as the carbonyl donor. We were pleased that nearly the same yield was obtained (entry 15).

The substrate scope was subsequently investigated under the optimized conditions. First, various benzaldehyde tosylhydrazone derivatives **1** were prepared and used for the carbonylation reaction; the results are summarized in Scheme 1.

Scheme 1. Carbonylation Reactions of Various Benzaldehyde Tosylhydrazone Derivatives[a]

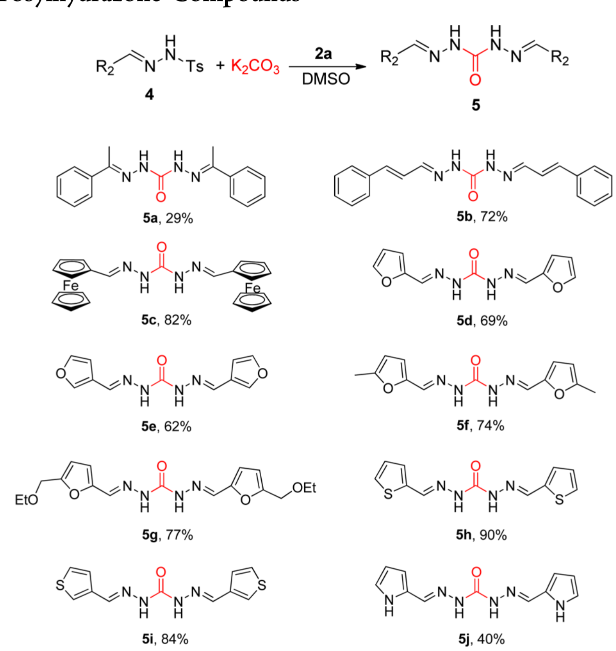


[a]Reaction conditions: **1** (0.5 mmol), K_2CO_3 (0.75 mmol), **2a** (0.5 mmol), DMSO (2 mL), 10 h, 60 °C, in air. Isolated yields.

Halogen-substituted substrates worked well, leaving halogen substituents untouched (**3b**−**3e**). *ortho*-Chlorophenyl tosylhydrazone also gave an excellent yield of the desired product **3e**, indicating that steric hindrance on the phenyl ring did not affect the results. Substrates with electron-donating substituents on the phenyl ring, such as alkyl, methoxyl, and dimethylamino groups, were also tested, affording the corresponding carbonylation products in excellent yields (**3f**−**3i**). The reaction also tolerated various functional groups such as nitro, cyano, and hydroxyl moieties; these substrates gave the desired products in good to excellent yields (**3j**−**3l**). Naphthaldehyde tosylhydrazone derivatives also underwent smooth transformation to give good product yields (**3m**, **3n**).

Next, we investigated the carbonylation reactions of other tosylhydrazone compounds. Scheme 2 summarizes the results.

Scheme 2. Carbonylation Reactions of Other Tosylhydrazone Compounds[a]



[a]Reaction conditions: **4** (0.5 mmol), K_2CO_3 (0.75 mmol), **2a** (0.5 mmol), DMSO (2 mL), 10 h, 60 °C, in air. Isolated yields.

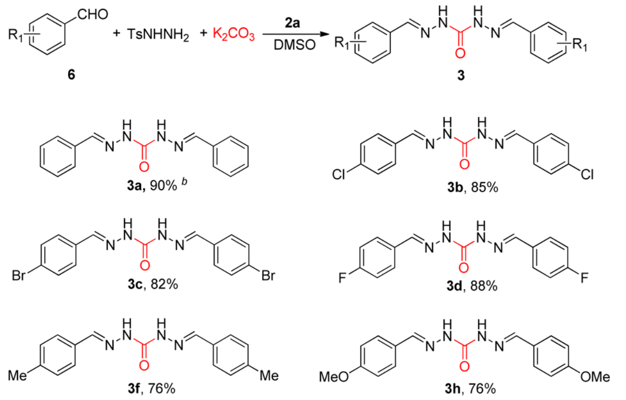
When acetophenone tosylhydrazone was used as the substrate under the optimized conditions, the product **5a** was obtained in poor yield (29%), indicating that the reaction was sensitive to steric effects at the α-position. Nonbenzaldehyde tosylhydrazones such as cinnamaldehyde and ferrocenecarboxaldehyde tosylhydrazones gave the desired products **5b** and **5c** in 74 and 86% yields, respectively. Several tosylhydrazone compounds based on heteroarenes were also successfully applied in the reaction (**5d**−**5j**), giving the desired products in moderate to excellent yields. These compounds provide a number of potential applications in coordination chemistry.

Because tosylhydrazones are readily prepared by mixing tosyl hydrazide with aldehydes, we investigated the one-pot carbonylation reactions of aldehydes, tosyl hydrazide, and K_2CO_3. All the reactants were added simultaneously, without the isolation of the intermediate tosylhydrazone or an increase in the reaction time. The carbonylation products were obtained in similar yields (Scheme 3). It is noteworthy that this reaction can be carried out on gram scale. For instance, upon combination of 10 mmol of the starting materials, product **3a** was obtained in 90% yield.

It is known that carbohydrazone compounds have strong intermolecular hydrogen bonds, and they are an important class of components for the self-assembly of supramolecular structures.[13] Slow evaporation of a colorless solution of **3a** in MeOH led to the formation of colorless needle crystals. Single crystal X-ray analysis shows that each unit cell contains two slightly different molecules conformations of **3a** (Figure 1).[14] Two molecules of **3a** of the same configuration (green in Figure 1) doubly interact by hydrogen bonding, and another molecule of **3a** (purple in Figure 1) is inserted into the gap.

A sample of **3a** at 0.5 wt % in $CHCl_3$ afforded a colorless solution. When ultrasound was applied to this solution for 1 min (at 0.40 W/cm^2 and 40 kHz), a white, immobile gel was produced (Figure 2a). The morphology of the resulting

Scheme 3. One-Pot Carbonylation Reactions[a]



[a]Reaction conditions: **6** (0.5 mmol), $TsNHNH_2$ (0.60 mmol), K_2CO_3 (0.75 mmol), **2a** (0.5 mmol), DMSO (2 mL), 10 h, 60 °C, in air, Isolated yields. [b]Carried out on 10 mmol scale.

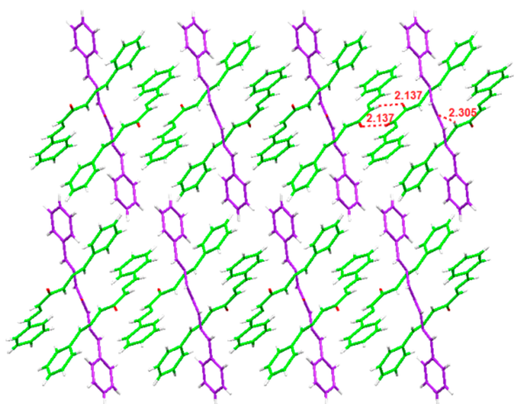


Figure 1. X-ray structure of **3a** (distances of hydrogen bond in Å).

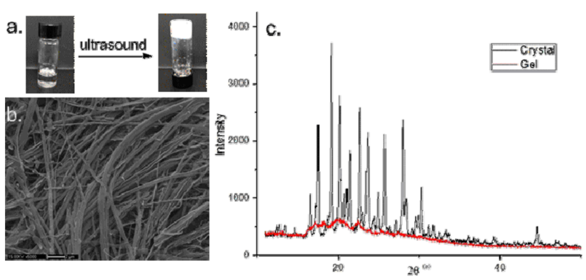
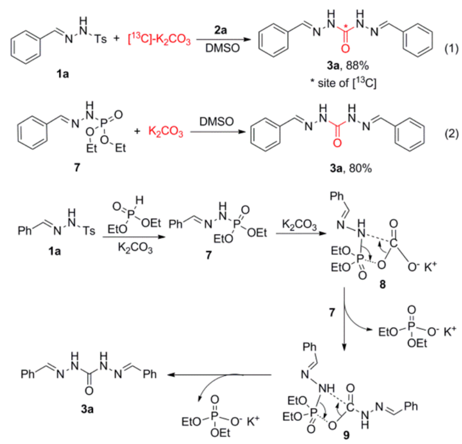


Figure 2. (a) Ultrasound induced gelation of **3a**. (b) SEM image of the xerogel obtained from the gel of **3a** in $CHCl_3$. (c) Powder X-ray diffraction patterns of the single crystal and gel (red line) of **3a**.

organogel was investigated by scanning electron microscopy (SEM), which shows the formation of entangled fibers with diameters of hundreds of nanometers (Figure 2b). The powder X-ray analysis of the xerogel prepared by air-drying the gel of **3a** in $CHCl_3$ was conducted and compared with the powder X-ray diffraction pattern of the crystals (Figure 2c), revealing an amorphous structure. Sonication probably causes the reorganization of the molecular assemblies, leading to the much longer entangled fibers, as shown in Figure 2b, that immobilize the solvent.

To ensure that the carbonyl donor was K_2CO_3 rather than an impurity, we investigated the reaction using K_2CO_3–^{13}C as the carbonyl donor under the optimized conditions (eq 1). We utilized ^{13}C NMR to examine the isolated product and clearly observed the incorporation of the ^{13}C–carbonyl. This confirmed that K_2CO_3 served as the carbonyl source for this reaction. The reaction did not proceed in the absence of phosphite; the tosylhydrazones coupled with phosphite to form phosphorohydrazones.[15] Therefore, a possible mechanism for this reaction was expected to start with the coupling of the tosylhydrazone with phosphite to form the phosphorohydrazone **7** (Scheme 4). Thereafter, the carbonate ion is trapped by

Scheme 4. Proposed Mechanism for the Reaction



7. Its C–O bonds are activated by phosphate.[16] Subsequently, the C–O bonds are cleaved in the acyl transfer process.[17] After two nucleophilic additions followed by an elimination process, the final product **3a** is obtained. To support this mechanistic proposal, phosphorohydrazone **7** was used as the substrate under the optimized conditions, and product **3a** was obtained in 80% yield (eq 2). This result was in agreement with the participation of a phosphorohydrazone as proposed in Scheme 4. Further studies to extend this chemistry and completely understand the transformation are underway.

In summary, we have reported a new carbonylation reaction of tosylhydrazones for the synthesis of 1,5-disubstituted carbohydrazones using K_2CO_3 as the carbonyl donor. The reaction system tolerates various functional groups and affords the desired products in good to excellent yields. To the best of our knowledge, this is the first example of a carbonylation reaction using K_2CO_3 as the carbonyl donor. Compared with other carbonylation agents, K_2CO_3 is inexpensive, readily available, ecologically friendly, and nongaseous. The developed reaction is expected to be a powerful tool for the synthesis of carbohydrazone compounds, which may have potential applications in supramolecular chemistry.

■ ASSOCIATED CONTENT

Supporting Information

X-ray crystallographic file in CIF format for compound **3a**, experimental details, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) CCDC 989592 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from www.ccdc.cam.ac.uk/data_request/cif.

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