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Green Synthetic Method for 1,5-Disubstituted Carbohydrazones

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Abstract: A green synthetic method for 1,5-disubstituted carbohydrazones is described. The reaction of dimethyl carbonate with hydrazine hydrate first gave carbohydrazide, which further reacted with various aromatic aldehydes or aliphatic ketones under solvent-free conditions to efficiently afford 1,5-disubstituted carbohydrazone. This protocol has the advantages of using nontoxic dimethyl carbonate as starting material, no use of organic solvents, short reaction time, high yield, and simple workup procedure.

Keywords: Carbohydrazide, carbohydrazone, dimethyl carbonate, solvent-free

INTRODUCTION

Dimethyl carbonate (DMC) can be used as a carbonylating, methylating, and methoxycarbonylating agent. Compared with general carbonylating or methylating agents, such as phosgene, dimethyl sulfate, and methyl halides, DMC is a nontoxic, environmentally benign reagent.[1] Therefore, it is necessary to explore the application of DMC in organic synthesis.

Hydrazone derivatives are reported to possess a wide range of biological activities, such as antituberculosis,[2] antimicrobial,[3] and anticonvulsant[4] activities. However, to the best of our knowledge, carbohydrazone derivatives

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are not reported anywhere. In continuation of our effort to explore the utilization of DMC and develop a green route for biologically active compounds, herein we report the synthesis of a series of 1,5-disubstituted carbohydrazones under solvent-free conditions using DMC as starting material.

RESULTS AND DISCUSSION

The commercially available DMC reacted with equivalent of hydrazine hydrate for 4 h to first give methyl hydrazinoformate as an intermediate via releasing methanol. After removing methanol from the reaction system, the intermediate further reacted with excess of hydrazine hydrate for another 4 h to give carbohydrazide (**1**) in 86% yield. It is important to note that the one-pot reaction of DMC with 2 equiv of hydrazine hydrate often leads to low yield of product. Removal of formed methanol from the reaction system is necessary for improving reaction yield.

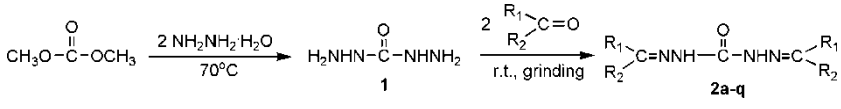
The resulting carbohydrazide (**1**) was ground with aromatic aldehydes or aliphatic ketones in a mortar with pestle at room temperature without any solvents for 2–8 min to afford 1,5-disubstituted carbohydrazones (**2a**–**q**) in very high yield (Scheme 1, Table 1).

It is noteworthy that the current method can be efficiently applied to all aromatic aldehydes, although the reaction rates of liquid aldehydes (**2a**, **2c**–**f**, and **2 k**–**n**) are faster than solid ones (**2b**, **2g**–**j**). For the aliphatic aldehyde, such as formaldehyde and acetaldehyde, the reactions often lead to products difficult to identify.

The current method can also be applied to aliphatic ketones. The less sterically hindered aliphatic ketones can readily react with carbohydrazide to give corresponding carbohydrazones in high yield (**2o**–**q**). However, the more hindered aromatic ketones, such as acetophenone, 4-methoxyacetophenone, and 4-chloroacetophenone, cannot give any desired products under similar conditions.

To compare the solvent-free method with solution method, the selected reactions were investigated using the conventional refluxing method in a solution of ethanol. However, the solution method takes much longer to complete the reactions, and the yields are often lower than the corresponding solvent-free reactions (Table 2).

The resulting compounds **2a**–**q** are highly soluble in hot DMF, slightly soluble in ethanol, and insoluble in acetone, chloroform, and dichloromethane.



Scheme 1.

Table 1. Green synthesis of compounds **2a–q**

Compound	R_1	R_2	Yield (%)[a]	Time (min)	Mp (°C)
2a	2-HO-C_6H_4	H	96	2	235–236
2b	4-HO-C_6H_4	H	94	6	220–224
2c	C_6H_5	H	97	3	210–212
2d	2-CH_3O-C_6H_4	H	97	3	197–198
2e	3-CH_3O-C_6H_4	H	97	4	187–188
2f	2-Cl-C_6H_4	H	92	3	212–214
2g	4-Cl-C_6H_4	H	94	6	244–246
2h	2,4-$Cl_2C_6H_3$	H	93	7	247–245
2i	3-CH_3O-4-OH-C_6H_3	H	90	8	235–236
2j	4-Br-C_6H_4	H	92	7	236–237
2k	4-C_2H_5O-C_6H_4	H	95	5	198–200
2l	4-(*n*-C_4H_9O)-C_6H_4	H	96	4	148–150
2m	4-(*n*-$C_6H_{13}O$)-C_6H_4	H	96	4	112–114
2n		H	95	5	184–186
2o	CH_3	CH_3	99	4	126–128
2p	$-(CH_2)_4-$		97	4	208–210
2q	$-(CH_2)_5-$		96	5	180–181

[a]Yields refer to isolated products.

All structures of the compounds **2a–q** were identified by ^{1}H NMR, IR, and elemental analyses. The IR spectra of compounds **2a–q** show the characteristic absorptions at 3087–3229 cm^{-1} for N-H and 1681–1718 cm^{-1} for C=O. The ^{1}H NMR spectra of compounds **2a–q** in DMSO-d_6 show proton peaks at $\delta = 9.32–10.84$ for NH and $\delta = 8.10–8.25$ for =CH.

Table 2. Comparison of the solvent-free method with the solution method

	Solution method		Solvent-free method	
Compd.	Time (h)	Yield (%)[a]	Time (min)	Yield (%)[a]
2a	4	87	2	96
2d	5	89	3	97
2f	5	85	3	92
2i	8	80	8	90
2j	7	81	7	92
2o	5	85	4	99
2q	6	86	5	96

[a]Yields refer to isolated products.

In conclusion, we have developed a green synthetic method for 1,5-disubstituted carbohydrazones in solvent-free conditions. This protocol has advantages of using the green reagent DMC as starting material, no use of organic solvents, mild reaction conditions, short reaction time, high yield, and simple workup procedure.

EXPERIMENTAL

IR spectra were recorded using KBr pellets on a Digilab 300 FTIR spectrophotometer and ^{1}H NMR spectra on a Mercury-400BB instrument using $(CD_3)_2SO$ as solvent and Me_4Si as internal standard. Elemental analyses were performed on a Vario E1 Elemental Analysis instrument. Mass spectra were recorded on a QP-1000A GC-MS using the impact mode (70 eV). Melting points were observed in an electrothermal melting-point apparatus and uncorrected.

Preparation of Carbohydrazide (1)

The mixture of DMC (0.09 mol) and hydrazine hydrate (0.10 mol) was stirred at 70°C for 4 h. The reaction was monitored by TLC. Then the librated methanol, water, and excess of DMC were removed under reduced pressure. To the residue, additional hydrazine hydrate (0.22 mol) was added. The mixture was stirred at 70°C for another 4 h. Then the resulting solution was distilled under reduced pressure until the white solid appeared; the residue was cooled slowly and the formed crystal was collected by filtration and dried to give product. Yield: 86%. Mp: 152–153°C.

General Procedure for the Preparation of 1,5-Disubstituted Carbohydrazones (2a–q)

The mixture of carbohydrazide (1 mmol) and an appropriate aromatic aldehyde or aliphatic ketone (2.2 mmol) was ground in a mortar by pestle at room temperature. After 2–8 min, the mixture was washed with acetone, and the solid was recrystallized from DMF-H_2O to give the product.

Data

2a: IR (KBr, ν, cm^{-1}): 3210, 3146 (N-H), 1700 (C═O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.77 (s, 2H, NH), 8.16 (s, 2H, ═CH), 6.63–7.02 (m, 8H, Ar-H). MS: m/z, 298 (M^+). Anal. calcd. for $C_{15}H_{14}N_4O_3$: C, 60.40; H, 4.73; N, 18.78. Found: C, 60.35; H, 4.68; N, 18.81.

2b: IR (KBr, ν, cm^{-1}): 3214, 3151 (N-H), 1703 (C═O). ^1H NMR (400 MHz, DMSO-d_6) δ 10.78 (s, 2H, NH), 8.17 (s, 2H, ═CH), 6.63–7.03 (m, 8H, Ar-H). MS: m/z, 298 (M^+). Anal. calcd. for $C_{15}H_{14}N_4O_3$: C, 60.40; H, 4.73; N, 18.78. Found: C, 60.45; H, 4.66; N, 18.74.

2c: IR (KBr, ν, cm^{-1}): 3202, 3134 (N-H), 1695 (C═O). ^1H NMR (400 MHz, DMSO-d_6) δ 10.74 (s, 2H, NH), 8.12 (s, 2H, ═CH), 6.60–7.00 (m, 10H, Ar-H). MS: m/z, 266 (M^+). Anal. calcd. for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.58; H, 5.27; N, 21.10.

2d: IR (KBr, ν, cm^{-1}): 3220, 3158 (N-H), 1707 (C═O). ^1H NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 2H, NH), 8.15 (s, 2H, ═CH), 6.90–7.35 (m, 8H, Ar-H), 3.79 (s, 6H, OCH_3). MS: m/z, 326 (M^+). Anal. calcd. for $C_{17}H_{18}N_4O_3$: C, 62.57; H, 5.56; N, 17.17. Found: C, 62.51; H, 5.50; N, 17.22.

2e: IR (KBr, ν, cm^{-1}): 3218, 3156 (N-H), 1706 (C═O). ^1H NMR (400 MHz, DMSO-d_6) δ 10.74 (s, 2H, NH), 8.14 (s, 2H, ═CH), 6.92–7.34 (m, 8H, Ar-H), 3.78 (s, 6H, OCH_3). MS: m/z, 326 (M^+). Anal. calcd. for $C_{17}H_{18}N_4O_3$: C, 62.57; H, 5.56; N, 17.17. Found: C, 62.64; H, 5.59; N, 17.12.

2f: IR (KBr, ν, cm^{-1}): 3216, 3153 (N-H), 1705 (C═O). ^1H NMR (400 MHz, DMSO-d_6) δ 10.79 (s, 2H, NH), 8.18 (s, 2H, ═CH), 6.64–7.05 (m, 8H, Ar-H). MS: m/z, 334 (M^+). Anal. calcd. for $C_{15}H_{12}Cl_2N_4O$: C, 53.75; H, 3.61; N, 16.72. Found: C, 53.67; H, 3.66; N, 16.68.

2g: IR (KBr, ν, cm^{-1}): 3217, 3154 (N-H), 1706 (C═O). ^1H NMR (400 MHz, DMSO-d_6) δ 10.79 (s, 2H, NH), 8.19 (s, 2H, ═CH), 6.65–7.06 (m, 8H, Ar-H). MS: m/z, 334 (M^+). Anal. calcd. for $C_{15}H_{12}Cl_2N_4O$: C, 53.75; H, 3.61; N, 16.72. Found: C, 53.84; H, 3.57; N, 16.77.

2h: IR (KBr, ν, cm^{-1}): 3229, 3166 (N-H), 1718 (C═O). ^1H NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 2H, NH), 8.25 (s, 2H, ═CH), 6.67–7.09 (m, 6H, Ar-H). MS: m/z, 402 (M^+). Anal. calcd. for $C_{15}H_{10}Cl_4N_4O$: C, 44.59; H, 2.49; N, 13.87. Found: C, 44.51; H, 2.53; N, 13.93.

2i: IR (KBr, ν, cm^{-1}): 3227, 3166 (N-H), 1715 (C═O). ^1H NMR (400 MHz, DMSO-d_6) δ 10.80 (s, 2H, NH), 8.20 (s, 2H, ═CH), 6.95–7.37 (m, 6H, Ar-H), 3.84 (s, 6H, OCH_3). MS: m/z, 358 (M^+). Anal. calcd. for $C_{17}H_{18}N_4O_5$: C, 56.98; H, 5.06; N, 15.63. Found: C, 56.91; H, 5.09; N, 15.57.

2j: IR (KBr, ν, cm^{-1}): 3223, 3160 (N-H), 1712 (C═O). ^1H NMR (400 MHz, DMSO-d_6) δ 10.81 (s, 2H, NH), 8.22 (s, 2H, ═CH), 6.66–7.07 (m, 8H, Ar-H).

MS: m/z, 422 (M^+). Anal. calcd. for $C_{15}H_{12}Br_2N_4O$: C, 42.48; H, 2.85; N, 13.21. Found: C, 42.55; H, 2.91; N, 13.16.

2k: IR (KBr, ν, cm^{-1}): 3219, 3157 (N-H), 1706 (C═O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74 (s, 2H, NH), 8.14 (s, 2H, ═CH), 6.88–7.33 (m, 8H, Ar-H), 4.04 (q, 4H, $^3J = 6.8$ Hz, OCH_2), 1.34 (t, 4H, ^{3}J = 6.8 Hz, CH_3). MS: m/z, 354 (M^+). Anal. calcd. for $C_{19}H_{22}N_4O_3$: C, 64.39; H, 6.26; N, 15.81. Found: C, 64.44; H, 6.20; N, 15.77.

2l: IR (KBr, ν, cm^{-1}): 3217, 3155 (N-H), 1704 (C═O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.72 (s, 2H, NH), 8.12 (s, 2H, ═CH), 6.85–7.30 (m, 8H, Ar-H), 4.00 (t, 4H, OCH_2), 1.34–1.73 (m, 8H, CH_2), 0.98 (t, 6H, CH_3). MS: m/z, 410 (M^+). Anal. calcd. for $C_{23}H_{30}N_4O_3$: C, 67.29; H, 7.37; N, 13.65. Found: C, 67.21; H, 7.43; N, 13.71.

2m: IR (KBr, ν, cm^{-1}): 3214, 3152 (N-H), 1702 (C═O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (s, 2H, NH), 8.10 (s, 2H, ═CH), 6.83–7.28 (m, 8H, Ar-H), 3.97 (t, 4H, OCH_2), 1.30–1.72 (m, 16H, CH_2), 0.97 (t, 6H, CH_3). MS: m/z, 466 (M^+). Anal. calcd. for $C_{27}H_{38}N_4O_3$: C, 69.50; H, 8.21; N, 12.01. Found: C, 69.43; H, 8.14; N, 12.10.

2n: IR (KBr, ν, cm^{-1}): 3203, 3135 (N-H), 1696 (C═O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 2H, NH), 8.13 (s, 2H, ═CH), 6.31–7.01 (m, 6H, Fu-H). MS: m/z, 246 (M^+). Anal. calcd. for $C_{11}H_{10}N_4O_3$: C, 53.66; H, 4.09; N, 22.75. Found: C, 53.58; H, 4.13; N, 22.83.

2o: IR (KBr, ν, cm^{-1}): 3197, 3094 (N-H), 1688 (C═O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (s, 2H, NH), 0.94 (s, 12H, CH_3). MS: m/z, 170 (M^+). Anal. calcd. for $C_7H_{14}N_4O$: C, 49.39; H, 8.29; N, 32.92. Found: C, 49.47; H, 8.33; N, 32.89.

2p: IR (KBr, ν, cm^{-1}): 3194, 3090 (N-H), 1686 (C═O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 2H, NH), 1.05–1.57 (m, 16H, CH_2). MS: m/z, 222 (M^+). Anal. calcd. for $C_{11}H_{18}N_4O$: C, 59.44; H, 8.16; N, 25.20. Found: C, 59.38; H, 8.20; N, 25.16.

2q: IR (KBr, ν, cm^{-1}): 3191, 3087 (N-H), 1681 (C═O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.32 (s, 2H, NH), 1.01–1.61 (m, 20H, CH_2). MS: m/z, 250 (M^+). Anal. calcd. for $C_{13}H_{22}N_4O$: C, 62.37; H, 8.86; N, 22.38. Found: C, 62.33; H, 8.82; N, 22.41.

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