

# Synthesis of acylhydrazines and, symmetrical and asymmetrical diacylhydrazines from carboxylic acid via the Vilsmeier reagent mediated process

Maarroof Zarei<sup>1</sup> · Maliheh Eslami Nakhli<sup>1</sup>

Received: 10 August 2016 / Accepted: 6 September 2016 / Published online: 21 September 2016  
© Springer Science+Business Media Dordrecht 2016

**Abstract** (Chloromethylene)dimethylammonium chloride (Vilsmeier reagent) has been used as an efficient and convenient reagent for the one-pot synthesis of acylhydrazines and symmetrical and asymmetrical diacylhydrazines from carboxylic acids. This reaction proceeded smoothly under mild conditions and it is quite practical, since the starting carboxylic acids can be easily handled and stored. Cleanliness, simplicity of the method and good to excellent yield of products are other advantages of this method.

**Keywords** Acylhydrazines · Diacylhydrazines · Vilsmeier reagent · One-pot · Hydrazine

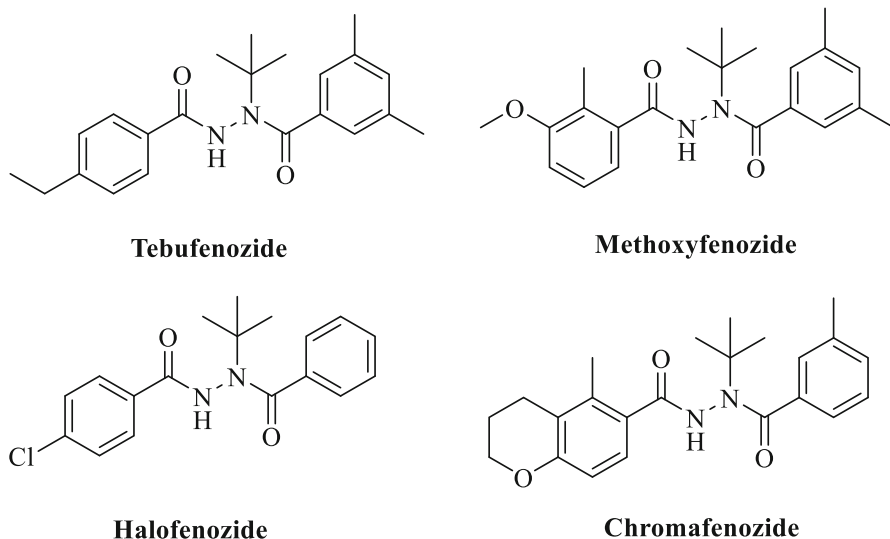
## Introduction

Acylhydrazines ( $RCONHNH_2$ ) and diacylhydrazines ( $RCONHNHCOR'$ ) have attracted considerable attention for decades as important organic synthons [1, 2]. Recently, many compounds containing these moieties have been reported which exhibit extensive application in biological activities such as antibacterial, antifungal [3], anticancer [4], herbicidal [5] and larvicidal [6] activities. *N-tert-Butyl-N,N'*-diacylhydrazines discovered by Rohm and Haas Co., with their high insecticidal activities and low toxicity to nontarget organisms such as mammals, have attracted considerable attention in recent years [7]. Tebufenozide, methoxyfenozide,

---

✉ Maarroof Zarei  
mzareei@hormozgan.ac.ir; maarroof1357@yahoo.com

<sup>1</sup> Department of Chemistry, Faculty of Sciences, University of Hormozgan, Bandar Abbas 71961, Iran



**Fig. 1** Commercial insecticides and pesticides contain diacylhydrazine moiety

halofenozide and chromafenozide are commercial insecticides and pesticides (Fig. 1).

Meanwhile, some compounds bearing a diacylhydrazine unit have been reported as polo-like kinase 1 (PLK1) [8] and malarial plasmepsin [9] inhibitors. It's worthy of attention that diacylhydrazines have been used as ligands to promote CuI-catalyzed C–N cross-coupling reactions of aryl bromides with *N*-heterocycles [10].

Generally, acylhydrazines can be obtained by reaction of hydrazine with acyl chlorides or esters [11, 12]. Reaction of acylhydrazines with acyl chlorides or esters has been commonly used for synthesis of diacylhydrazines [13, 14].

Some acyl halides are not commercially available, difficult to prepare or unstable. To promote this transformation from carboxylic acid, some acid activators have been used, including DCC [15], polyphosphoric acid [16] and  $\text{PhOPCl}_2$  [17]. But some of these reagents are expensive, not readily available, hygroscopic and moisture-sensitive. Low yield, unnecessary waste and painful chromatographic separation are other disadvantages of these reagents.

(Chloromethylene)dimethylammonium chloride (Vilsmeier reagent) **1** has been found to be useful in formylation, dehydration, chlorination, and other reactions [18–21]. It has also emerged as a convenient reagent in the synthesis of  $\beta$ -sultams [22] and  $\beta$ -lactams [23–25]. Vilsmeier reagent is easily prepared as a white solid by reaction of *N,N*-dimethylformamide (DMF) and chlorinating agents such as  $(\text{COCl}_2)$  or  $\text{SOCl}_2$  in dry  $\text{CH}_2\text{Cl}_2$  [23]. This reagent can be kept for a long time by storage in a well-capped bottle which is also commercially available.

In this paper, we described the use of Vilsmeier reagent as an efficient and versatile reagent for one-pot synthesis of acylhydrazines and symmetrical and asymmetrical diacylhydrazines from carboxylic acids.

## Experimental

### Materials and methods

All required chemicals were purchased from Merck, Aldrich and Acros chemical companies. The melting points were determined on a silicone oil bath and are uncorrected. IR spectra were measured on a galaxy series FT-IR 5000 spectrometer. NMR spectra were recorded in DMSO- $d_6$  using a Bruker spectrophotometer ( $^1\text{H}$  NMR 300 MHz,  $^{13}\text{C}$  NMR 75 MHz) using tetramethylsilane as an internal standard, and coupling constants were given in cycles per second (Hz). Elemental analyses were run on a Vario EL III elemental analyzer. Thin-layer chromatography (TLC) was carried out on silica gel 254 analytical sheets obtained from Fluka.

#### *General procedure for synthesis of acylhydrazines 2–5*

A solution of carboxylic acid (1.0 mmol), Vilsmeier reagent (1.0 mmol) and  $\text{Et}_3\text{N}$  (3.0 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (10 mL) at room temperature was added to a solution of hydrazine hydrate (4.0 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (5 mL) and the mixture was stirred 7 h. The mixture was washed successively with saturated  $\text{NaHCO}_3$  (15 mL) and brine (15 mL). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ), filtered and the solvent was removed under reduced pressure to give the crude products. The crude residues were purified by crystallization from ethanol 95 %. Spectral data for **2–5** have been previously reported [26–29].

#### *General procedure for synthesis of symmetrical diacylhydrazines 6–16*

Hydrazine hydrate (0.2 mmol) was added to a solution of carboxylic acid (1.0 mmol), Vilsmeier reagent (1.0 mmol) and  $\text{Et}_3\text{N}$  (4.0 mmol) in dry  $\text{CH}_3\text{CN}$  (15 mL) at room temperature and the mixture was stirred 7 h. Saturated  $\text{NaHCO}_3$  (15 mL) was added and the mixture was extracted with  $\text{EtOAc}$  ( $3 \times 15$  mL). The organic layer was washed with brine (20 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and the solvent was removed under reduced pressure to give the crude products. The crude residues were purified by crystallization from ethanol 95 %. Spectral data for **6–7**, **10**, **13** and **15** have been previously reported [30–34].

*2-(4-Chlorophenoxy)-N'-(2-(4-chlorophenoxy)acetyl)acetohydrazide (8)* White solid. mp: 130–132 °C. IR (KBr)  $\text{cm}^{-1}$ : 1633 (CO), 3294 (NH);  $^1\text{H}$  NMR  $\delta$  4.70 (2 $\text{CH}_2$ , s, 4H), 6.78–7.28 (ArH, m, 8H), 9.86 (2NH, s, 2H);  $^{13}\text{C}$  NMR  $\delta$  65.4 ( $\text{CH}_2$ ), 115.9, 127.1, 129.3, 157.2 (aromatic carbons), 168.7 (CO). Anal. Calcd for  $\text{C}_{16}\text{H}_{14}\text{Cl}_2\text{N}_2\text{O}_4$ : C, 52.05; H, 3.82; N, 7.59. Found: C, 52.18; H, 3.93; N, 7.67.

*2-(1,3-Dioxoisindolin-2-yl)-N'-(2-(1,3-dioxoisindolin-2-yl)acetyl)acetohydrazide (9)* Off-white solid. mp  $>210$  °C. IR (KBr)  $\text{cm}^{-1}$ : 1640 (CO), 1735, 1776 (CO, Phth), 3330 (NH);  $^1\text{H}$  NMR  $\delta$  4.22 (2 $\text{CH}_2$ , s, 4H), 7.47–7.70 (ArH, m, 8H), 9.55 (2NH, s, 2H);  $^{13}\text{C}$  NMR  $\delta$  46.1 ( $\text{CH}_2$ ), 125.0, 132.0, 132.4 (aromatic carbons),

168.7 (CO, phth), 170.4 (CO). Anal. Calcd for  $C_{20}H_{14}N_4O_6$ : C, 59.12; H, 3.47; N, 13.79. Found: C, 59.28; H, 3.60; N, 13.86.

*3-Hydroxy-N'-(3-hydroxy-2-naphthoyl)-2-naphthohydrazide (11)* White solid. mp: 153–155 °C IR (KBr)  $cm^{-1}$ : 1639 (CO), 3050–3397 (OH), 3415 (NH);  $^1H$  NMR  $\delta$  7.34–7.91 (ArH, m, 12H), 9.93 (2NH, s, 2H), 11.33 (2OH, s, 2H);  $^{13}C$  NMR  $\delta$  113.1, 121.6, 123.4, 126.7, 128.8, 130.2, 130.4, 132.5, 136.6, 155.4 (aromatic carbons), 165.3 (CO). Anal. Calcd for  $C_{22}H_{16}N_2O_4$ : C, 70.96; H, 4.33; N, 7.52. Found: C, 71.06; H, 4.43; N, 7.47.

*3-Hydroxy-N'-(3-hydroxybenzoyl)benzohydrazide (12)* White solid. mp: 99–101 °C. IR (KBr)  $cm^{-1}$ : 1632 (CO), 3154–3659 (NH, OH);  $^1H$  NMR  $\delta$  6.93–7.47 (ArH, m, 8H), 10.43 (2NH, s, 2H), 11.59 (2OH, s, 2H);  $^{13}C$  NMR  $\delta$  114.3, 120.7, 122.1, 130.5, 133.8, 157.2 (aromatic carbons), 166.7 (CO). Anal. Calcd for  $C_{14}H_{12}N_2O_4$ : C, 61.76; H, 4.44; N, 10.29. Found: C, 61.68; H, 4.50; N, 10.22.

*N'-(2,6-Dimethoxybenzoyl)-2,6-dimethoxybenzohydrazide (14)* Off-white solid. mp: 158–160 °C. IR (KBr)  $cm^{-1}$ : 1637 (CO), 3441 (NH);  $^1H$  NMR  $\delta$  3.71 (4 OMe, s, 12H), 6.77–7.45 (ArH, m, 6H), 9.72 (2NH, s, 2H);  $^{13}C$  NMR  $\delta$  55.4 (CH<sub>3</sub>), 123.4, 128.5, 133.9, 148.5 (aromatic carbons), 166.9 (CO). Anal. Calcd for  $C_{18}H_{20}N_2O_6$ : C, 59.99; H, 5.59; N, 7.77. Found: C, 60.11; H, 5.74; N, 7.70.

*2-Methoxy-N'-(2-methoxyacetyl)acetohydrazide (16)* White solid. mp: 52–54 °C. IR (KBr)  $cm^{-1}$ : 1644 (CO), 3227 (NH);  $^1H$  NMR  $\delta$  3.29 (2OMe, s, 6H), 4.14 (2CH<sub>2</sub>, s, 4H), 9.35 (2NH, s, 2H);  $^{13}C$  NMR  $\delta$  58.7 (OMe), 70.0 (CH<sub>2</sub>), 171.8 (CO). Anal. Calcd for  $C_6H_{12}N_2O_4$ : C, 40.91; H, 6.87; N, 15.90. Found: C, 41.04; H, 6.99; N, 15.96.

#### General procedure for synthesis of asymmetrical diacylhydrazines 17–26

Acylhydrazines **2–5** (1.0 mmol) was added to a solution of carboxylic acid (1.5 mmol), Vilsmeier reagent (1.5 mmol) and Et<sub>3</sub>N (5.0 mmol) in dry CH<sub>3</sub>CN (15 mL) at room temperature and the mixture was stirred 6 h. Saturated NaHCO<sub>3</sub> (20 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL). The organic layer was washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and the solvent was removed under reduced pressure to give the crude products. The crude residues were purified by crystallization from ethanol 95 %. The data for **19** has been previously reported [35].

*2-(4-Chlorophenoxy)-N'-(2-phenoxyacetyl)acetohydrazide (17)* White solid. mp: 130–132 °C. IR (KBr)  $cm^{-1}$ : 1635 (CO), 3199 (NH);  $^1H$  NMR  $\delta$  4.61, 4.64 (2 CH<sub>2</sub>, 2 s, 4H), 6.84–7.32 (ArH, m, 9H), 9.72, 9.87 (2 NH, 2 s, 2H);  $^{13}C$  NMR  $\delta$  60.3, 65.9 (CH<sub>2</sub>) 115.9, 116.0, 122.3, 126.9, 129.0, 129.5, 157.1, 159.4 (aromatic carbons) 168.9, 176.4 (CO). Anal. Calcd for  $C_{16}H_{15}ClN_2O_4$ : C, 57.41; H, 4.52; N, 8.37. Found: C, 57.55; H, 4.69; N, 8.44.

*2-Methoxy-N'-(2-phenoxyacetyl)acetohydrazide (18)* White solid. mp: 81–83 °C. IR (KBr)  $cm^{-1}$ : 1639 (CO), 3214 (NH);  $^1H$  NMR  $\delta$  3.32 (OMe, s, 3H), 4.19, 4.73 (2

CH<sub>2</sub>, 2 s, 4H), 6.79–7.25 (ArH, m, 5H), 9.59, 9.63 (2 NH, 2 s, 2H); <sup>13</sup>C NMR δ 57.7 (OMe), 66.2, 69.7 (CH<sub>2</sub>), 115.9, 122.5, 129.6, 159.3 (aromatic carbons), 169.1, 172.2 (CO). Anal. Calcd for C<sub>11</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.41; H, 6.03; N, 11.70.

*2-(4-Chlorophenoxy)-N'-(2-(2,4-dichlorophenoxy)acetyl)acetohydrazide (20)* White solid. mp: 146–148 °C. IR (KBr) cm<sup>-1</sup>: 1636 (CO), 3217 (NH); <sup>1</sup>H NMR δ 4.69, 4.80 (2 CH<sub>2</sub>, 2 s, 4H), 6.90–7.45 (ArH, m, 7H), 9.50, 10.10 (2 NH, 2 s, 2H); <sup>13</sup>C NMR δ 65.6, 65.9 (CH<sub>2</sub>), 115.5, 117.2, 125.7, 127.1, 128.4, 128.7, 129.2, 130.8, 153.5, 157.4 (aromatic carbons), 169.0, 174.1 (CO). Anal. Calcd for C<sub>16</sub>H<sub>13</sub>Cl<sub>3</sub>N<sub>2</sub>O<sub>4</sub>: C, 47.61; H, 3.25; N, 6.94. Found: C, 47.55; H, 3.13; N, 6.86.

*2-(2,4-Dichlorophenoxy)-N'-(2-methoxyacetyl)acetohydrazide (21)* White solid. mp: 77–79 °C. IR (KBr) cm<sup>-1</sup>: 1637 (CO), 3225 (NH); <sup>1</sup>H NMR δ 3.44 (OMe, s, 3H), 4.14, 4.75 (2 CH<sub>2</sub>, 2 s, 4H), 6.71–7.34 (ArH, m, 3H), 9.15, 9.37 (2 NH, 2 s, 2H); <sup>13</sup>C NMR δ 58.8 (OMe), 65.9, 69.0 (CH<sub>2</sub>), 117.3, 125.3, 128.5, 128.8, 130.8, 153.3 (aromatic carbons), 168.0, 171.0 (CO). Anal. Calcd for C<sub>11</sub>H<sub>12</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>4</sub>: C, 43.02; H, 3.94; N, 9.12. Found: C, 43.15; H, 4.11; N, 9.20.

*2-(Naphthalen-2-yloxy)-N'-(2-phenoxyacetyl)acetohydrazide (22)* White solid. mp: 142–144 °C. IR (KBr) cm<sup>-1</sup>: 1650 (CO), 3216 (NH); <sup>1</sup>H NMR δ 4.60, 4.72 (2 CH<sub>2</sub>, 2 s, 4H), 6.96–7.87 (ArH, m, 12H), 9.65, 9.74 (2 NH, 2 s, 2H); <sup>13</sup>C NMR δ 64.0, 65.3 (CH<sub>2</sub>), 109.9, 115.7, 117.6, 121.5, 124.0, 127.2, 127.3, 128.7, 129.4, 129.5, 131.1, 135.2, 156.1, 159.2 (aromatic carbons), 168.7, 175.6 (CO). Anal. Calcd for C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.64; H, 5.31; N, 7.92.

*2-(4-Chlorophenoxy)-N'-(2-(naphthalen-2-yloxy)acetyl)acetohydrazide (23)* White solid. mp: 146–148 °C. IR (KBr) cm<sup>-1</sup>: 1638 (CO), 3246 (NH); <sup>1</sup>H NMR δ 4.63, 4.80 (2 CH<sub>2</sub>, 2 s, 4H), 6.85–7.56 (ArH, m, 11H), 9.49, 9.63 (2 NH, 2 s, 2H); <sup>13</sup>C NMR δ 60.4, 65.4 (CH<sub>2</sub>), 110.0, 116.0, 117.6, 124.0, 127.1, 127.2, 127.3, 128.8, 129.3, 129.4, 131.1, 135.2, 156.0, 157.2 (aromatic carbons), 168.7, 174.3 (CO). Anal. Calcd for C<sub>20</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>4</sub>: C, 62.42; H, 4.45; N, 7.28. Found: C, 62.51; H, 4.58; N, 7.23.

*2-(2,4-Dichlorophenoxy)-N'-(2-(naphthalen-2-yloxy)acetyl)acetohydrazide (24)* White solid. mp: 170–172 °C. IR (KBr) cm<sup>-1</sup>: 1643 (CO), 3225 (NH); <sup>1</sup>H NMR δ 4.72, 4.81 (2 CH<sub>2</sub>, 2 s, 4H), 6.79–8.00 (ArH, m, 10H), 9.96, 9.97 (2 NH, 2 s, 2H); <sup>13</sup>C NMR δ 65.6, 65.9 (CH<sub>2</sub>), 117.2, 117.7, 123.9, 125.6, 127.1, 127.2, 127.3, 127.4, 128.5, 128.6, 128.7, 129.3, 130.8, 131.0, 135.0, 156.0 (aromatic carbons), 168.6, 175.5 (CO). Anal. Calcd for C<sub>20</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>4</sub>: C, 57.30; H, 3.85; N, 6.68. Found: C, 57.25; H, 3.94; N, 6.71.

*2-Methoxy-N'-(2-(naphthalen-2-yloxy)acetyl)acetohydrazide (25)* White solid. mp: 158–160 °C. IR (KBr) cm<sup>-1</sup>: 1649 (CO), 3254 (NH); <sup>1</sup>H NMR δ 3.36 (OMe, s, 3H), 4.16, 4.80 (2 CH<sub>2</sub>, 2 s, 4H), 7.05–7.75 (ArH, m, 7H), 9.35, 9.94 (2 NH, 2 s, 2H); <sup>13</sup>C NMR δ 58.8 (OMe), 65.3, 69.7 (CH<sub>2</sub>), 109.7, 117.8, 124.4, 127.0, 127.3, 128.8, 129.4, 131.1, 135.1, 156.3 (aromatic carbons), 168.8, 171.7

(CO). Anal. Calcd for  $C_{15}H_{16}N_2O_4$ : C, 62.49; H, 5.59; N, 9.72. Found: C, 62.62; H, 5.75; N, 9.80.

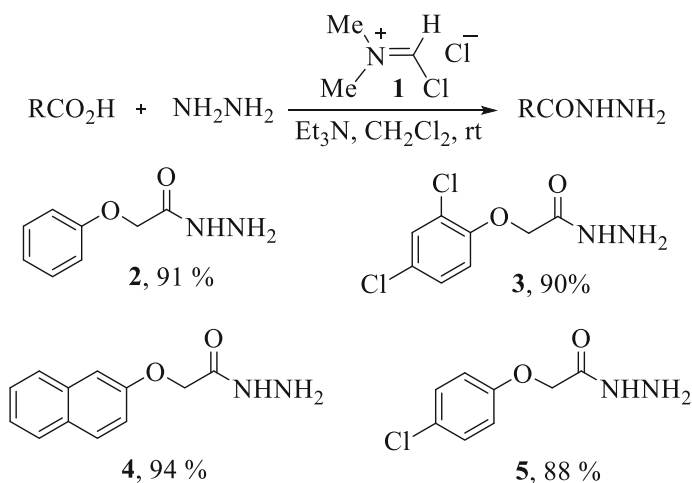
2-(4-Chlorophenoxy)-*N'*-(2-methoxyacetyl)acetohydrazide (**26**) White solid. mp: 114–116 °C. IR (KBr)  $cm^{-1}$ : 1631 (CO), 3228 (NH);  $^1H$  NMR  $\delta$  3.32 (OMe, s, 3H), 4.17, 4.79 (2 CH<sub>2</sub>, 2 s, 4H), 6.74–7.27 (ArH, m, 4H), 8.58, 8.62 (2 NH, 2 s, 2H);  $^{13}C$  NMR  $\delta$  57.4 (OMe), 66.1, 68.2 (CH<sub>2</sub>), 115.9, 127.2, 129.4, 157.3 (aromatic carbons), 168.7, 171.7 (CO). Anal. Calcd for  $C_{11}H_{13}ClN_2O_4$ : C, 48.45; H, 4.81; N, 10.27. Found: C, 48.58; H, 4.97; N, 10.21.

## Results and discussion

Reaction of carboxylic acids with Vilsmeier reagent in the absence of any nucleophile gives acyl chlorides [36]. Initially, we set up a model reaction with phenoxyacetic acid (1 mmol), triethylamine (3 mmol), Vilsmeier reagent **1** (1 mmol), and hydrazine hydrate (4 mmol) in dry dichloromethane at room temperature. After workup and crystallization from ethyl acetate, 2-phenoxyacetohydrazide **2** was obtained at a 91 % yield. According to this result, acylhydrazines **2–5** were prepared in one stage from carboxylic acids with excellent yields (Scheme 1).

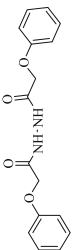
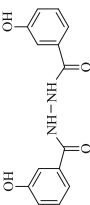
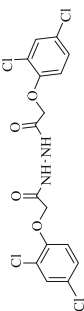

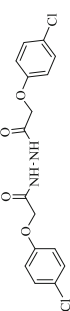
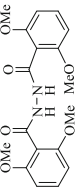
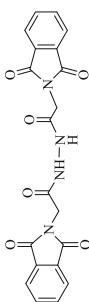
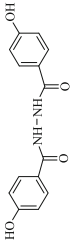
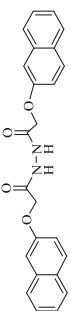
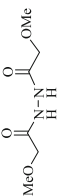
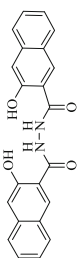
In this method acylhydrazines are formed not from the acyl halides or esters but directly from the carboxylic acids. The by-products are DMF and triethylamine hydrochloride salt which both are easily removed by aqueous workup.

Preparation of diacylhydrazines from acylhydrazines by the general procedure and successful results obtained from one-pot synthesis of acylhydrazines promoted us to undertake one-pot synthesis of symmetrical diacylhydrazines directly from the carboxylic acids. Treatment of phenoxyacetic acid, triethylamine and Vilsmeier reagent **1** with hydrazine hydrate in dry dichloromethane at room temperature gave 2-phenoxy-*N'*-(2-phenoxyacetyl)-acetohydrazide **6** at a low yield. This reaction was

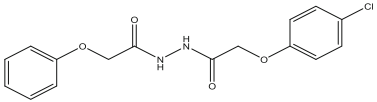
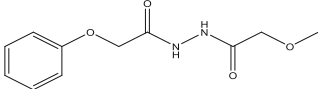
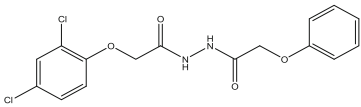
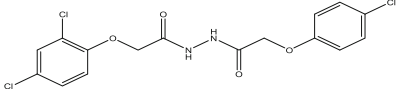
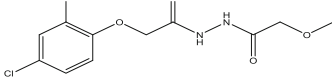
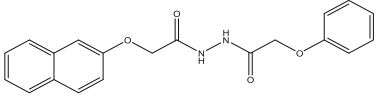
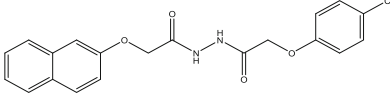
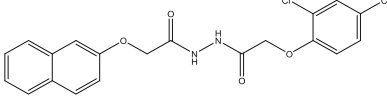
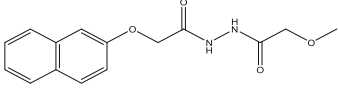
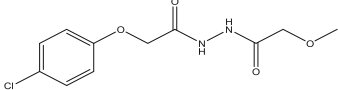


**Scheme 1** Synthesis of acylhydrazines **2–5**

**Table 1** One-pot synthesis of symmetrical diacylhydrazines **6–16** from carboxylic acids


Compound no.	Diacylhydrazine	Yield (%)	Compound no.	Diacylhydrazine	Yield (%)
<b>6</b>		89	<b>12</b>		98
<b>7</b>		86	<b>13</b>		88
<b>8</b>		91	<b>14</b>		86
<b>9</b>		83	<b>15</b>		80
<b>10</b>		89	<b>16</b>		93
<b>11</b>		85			

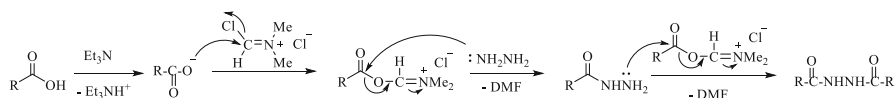
**Table 2** Synthesis of asymmetrical diacylhydrazines **17–26**

		$\text{RCONHNH}_2 + \text{R}'\text{CO}_2\text{H} \xrightarrow[\text{CH}_3\text{CN, rt}]{\text{1, Et}_3\text{N}} \text{RCONHHCOR}'$			
		2-5			17-26
Entry	Acylhydrazine	Compound no.	Diacylhydrazine	Yield (%)	
1	2	17		84	
2	2	18		81	
3	3	19		84	
4	3	20		85	
5	3	21		88	
6	4	22		87	
7	4	23		91	
8	4	24		93	
9	4	25		82	
10	5	26		87	

performed in dry acetonitrile and the mixture was washed with saturated sodium hydrogen carbonate. Extraction by ethyl acetate and crystallization from ethanol gave diacylhydrazine **6** with an 89 % yield.

Symmetrical diacylhydrazine **6–16** were synthesized by this method from corresponding carboxylic acids and hydrazine (Table 1). Progress of reactions was checked by TLC monitoring. All products were confirmed by spectral data.





**Scheme 2** Proposed mechanism

Acylhydrazines **2–5** were reacted with a solution of corresponding carboxylic acids, triethylamine and reagent **1** in dry acetonitrile. Asymmetrical diacylhydrazines **17–26** were obtained with good to excellent yields after usual work up and crystallization from ethanol 95 % (Table 2). In this method, Vilsmeier reagent is a versatile and convenient reagent because of reducing by-product formation and a simplifying work-up.

According to the reported mechanism in the literature for [22], the mechanism below is proposed (Scheme 2).

## Conclusion

In summary, Vilsmeier reagent serves as a convenient and effective reagent for synthesis of acylhydrazines. In addition, one-pot synthesis provides easy and versatile methods for obtaining pure symmetrical and asymmetrical diacylhydrazines in good to excellent yields under simple and mild conditions. The use of Vilsmeier reagent eliminates the need to handle and prepare acyl halides. This method is very efficient particularly for larger-scale applications because the side-products (DMF and triethylamine hydrochloride salt) are easily removed by aqueous work-up.

**Acknowledgments** The authors thank the University of Hormozgan Research Council for financial support of this work.

## References

1. A. Kudelko, M. Wroblowska, *Tetrahedron Lett.* **55**, 3252 (2014)
2. K. Jasiak, A. Kudelko, *Tetrahedron Lett.* **56**, 5878 (2015)
3. M. Zareef, R. Iqbal, B. Mirza, K.M. Khan, A. Manan, F. Asim, S.W. Khan, *Arkivoc* (ii), 141 (2008)
4. C. Zi-Ning, H. Juan, L. Ying, L. Yun, Y. Xin-Ling, C. Fu-Heng, *Chin. J. Chem.* **26**, 916 (2008)
5. X.-H. Liu, L. Pan, Y. Ma, J.-Q. Weng, C.-X. Tan, Y.-H. Li, Y.-X. Shi, B.-J. Li, Z.-M. Li, Y.-G. Zhang, *Chem. Biol. Drug Des.* **78**, 689 (2011)
6. H. Runqiu, W. Qingmin, *J. Organomet. Chem.* **637–639**, 94 (2001)
7. H. Wang, Z. Yang, Z. Fan, Q. Wu, Y. Zhang, N. Mi, S. Wang, Z. Zhang, H. Song, F. Liu, *J. Agric. Food Chem.* **59**, 628 (2001)
8. J. Sun, P.-C. Lv, F.-J. Guo, X.-Y. Wang, X. Han, Y. Zhang, G.-H. Sheng, S.-S. Qian, H.-L. Zhu, *Eur. J. Med. Chem.* **81**, 420 (2014)
9. K. Ersmark, M. Nervall, E. Hamelink, L.K. Janka, J.C. Clemente, B.M. Dunn, M.J. Blackman, B. Samuelsson, J. Aqvist, A. Hallberg, *J. Med. Chem.* **48**, 6090 (2005)
10. L. Li, L. Zhu, D. Chen, X. Hu, R. Wang, *Eur. J. Org. Chem.* **2011**, 2692 (2011)
11. X. Yu, L. Shi, S. Ke, *Bioorg. Med. Chem. Lett.* **25**, 5772 (2015)
12. P.R. Kamath, D. Sunil, A.A. Ajees, *Res. Chem. Intermed.* **42**, 5899 (2016)
13. A.-F. Li, Y.-B. Ruan, Q.-Q. Jiang, W.-B. He, Y.-B. Jiang, *Chem. Eur. J.* **16**, 5794 (2010)
14. D. Wang, W. Chena, Y. Zheng, C. Dai, L. Wang, B. Wang, *Heterocycl. Commun.* **19**, 171 (2013)

15. Y. Qian, Z. Lu, C. Lu, Z. Chen, Y. Cui, *Dyes Pigments* **75**, 641 (2007)
16. R.F.M. Elshaarawy, C. Janiak, *Z. Naturforsch.* **66**, 1202 (2011)
17. C.I. Chiriac, *Rev. Roum. Chim.* **27**, 411 (1982)
18. A. Jarrahpour, M. Zarei, *Tetrahedron Lett.* **48**, 8712 (2007)
19. W.-B. Huang, C.-Y. Du, J.-A. Jiang, Y.-F. Ji, *Res. Chem. Intermed.* **39**, 2849 (2013)
20. L. Pellegatti, S.L. Buchwald, *Org. Process Res. Dev.* **16**, 1442 (2012)
21. H. Yu, Y. Zhang, T. Li, P. Liao, Q. Diao, G. Xin, Q. Meng, D. Hou, *RSC Adv.* **5**, 11293 (2015)
22. M. Zarei, A. Jarrahpour, *J. Heterocycl. Chem.* **50**, 438 (2013)
23. A. Jarrahpour, M. Zarei, *Tetrahedron* **65**, 2927 (2009)
24. A. Jarrahpour, A. Fadavi, M. Zarei, *Bull. Chem. Soc. Jpn* **84**, 320 (2011)
25. M. Zarei, M. Mohamadzadeh, *Tetrahedron* **67**, 5832 (2011)
26. D. Kaushik, S.A. Khan, G. Chawla, S. Kumar, *Eur. J. Med. Chem.* **45**, 3943 (2010)
27. W. Shi, X. Qian, R. Zhang, G. Song, *J. Agric. Food Chem.* **49**, 124 (2001)
28. A. Husain, A. Ahmad, M.M. Alam, M. Ajmal, P. Ahuja, *Eur. J. Med. Chem.* **44**, 3798 (2009)
29. H.M. Abdel Hamid, E.S. Ramadan, M. Hagar, E.S. El Ashry, *Synth. Commun.* **34**, 377 (2004)
30. M.J. Fray, K. Cooper, M.J. Parry, R. Kenneth, J. Steele, *J. Med. Chem.* **38**, 3514 (1995)
31. Z.Q. Yuan, H. Ishikawa, D.L. Boger, *Org. Lett.* **7**, 741 (2005)
32. R. Palit, N. Saraswat, J. Saraswat, *Int. Res. J. Pharm.* **7**, 1 (2016)
33. V.K. Tandon, R.B. Chhor, *Synth. Commun.* **31**, 1727 (2001)
34. Salahuddin, M. Shaharyar, A. Mazumder, M.J. Ahsan, *Arabi. J. Chem.* **7**, 418 (2014)
35. D. Dovlatyan, *Izv. Akad. Nauk Arm. SSR Khim. Nauki.* **15**, 151 (1962)
36. H. Eilingsfeld, M. Seefelder, H. Weidinger, *Angew. Chem.* **72**, 836 (1960)