

# Protection-, Salt-, and Metal-Free Syntheses of [n]-Shogaols by Use of Dimethylammonium Dimethyl Carbamate (DIMCARB) without Protecting Groups

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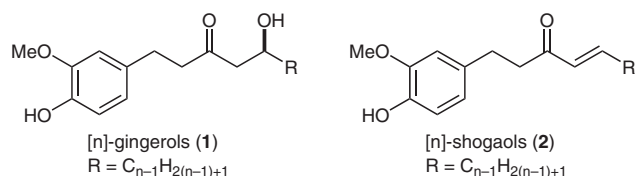
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**Abstract:** Shogaols, the pungent principle of ginger, exhibit interesting bioactivities. Practical preparation of shogaols is highly desired. Here we report the protection/deprotection-, salt-, and metal-free synthesis of shogaol in three steps by use of dimethylammonium dimethyl carbamate (DIMCARB), in which DIMCARB smoothly promoted Mannich-type condensation of the ketone donor with the aldehyde acceptor through the iminium cation intermediate.

**Key words:** shogaols, protection-free synthesis, salt-free synthesis, metal-free synthesis, cross Mannich-type condensation

The pungent principles of fresh ginger are homologous phenolic ketones known as gingerols **1**, which are converted to dehydration products as shogaols **2** during storage or thermal processing (Figure 1). Shogaols **2** are more pungent than gingerols **1**; in addition, recently interesting bioactivities are reported. For example, *trans*-[8]-shogaol showed the highest antifouling activity comparable with that of tributyltin fluoride (TBTF), which is recognized as one of the most effective antifouling agents, in the conventional submerged assay.<sup>1</sup> Further, [6]-shogaol was more effective than [6]-gingerol in inhibition of PG synthase.<sup>2</sup>

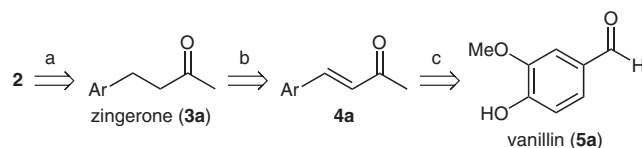


**Figure 1** [n]-Gingerols **1** and [n]-shogaols **2**

Previous syntheses of shogaols **2** contain following problems: (1) multistep synthesis, (2) use of strong base, (3) low temperature, and (4) wastes, such as salt.<sup>3</sup> Modern organic synthesis highly required environmentally friendly procedure. Herein, we report protection/deprotection-, salt-, and metal-free synthesis of shogaols **2** under neutral condition at 25 °C in three steps as shown in Scheme 1. Benzalacetone derivative **4a** is generated from vanillin (**5a**) employing a direct Mannich-type condensation.

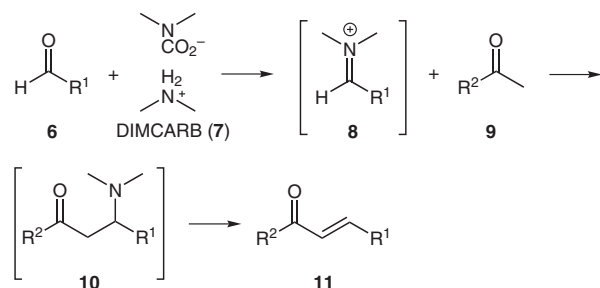
Zingerone (**3a**) is obtained by chemoselective reduction of **4a**. Second direct Mannich-type condensation of **3a** with aldehyde furnished shogaols **2**.

Recently, organic transformations via iminium and/or enamine intermediate catalyzed by metal-free small organic molecule have received great attention by organic chemists because of its high versatility, maneuverability, simplicity, and safety.<sup>4</sup> In general, protection of the functional group is not required in most of organocatalytic reactions; therefore, we took these advantages to synthesize shogaols **2**. Iminium cation mediated Mannich-type condensation is one of the promising synthetic methods for direct preparation of benzalacetone derivatives of aldehydes and enolizable ketones. Kreher and Strauss reported that dimethylammonium dimethyl carbamate (DIMCARB, **7**) is a recyclable reaction medium and as a catalyst for preparation of benzalacetone derivatives.<sup>5</sup> As shown in Scheme 2, iminium cation intermediate **8** in situ derived from the aldehyde **6** and DIMCARB **7** undergoes Mannich-type condensation with the ketone **9**. Subsequent elimination of dimethylamine from the Mannich adduct **10** is facile and gives the benzalacetone derivative **11**. In spite of their useful findings, this procedure was employed in only a few papers.<sup>6</sup> Strong bases, such as sodium hydroxide, are usually employed to prepare benzalacetone derivatives in most cases, though formation of dibenzalacetone derivatives is unavoidable.



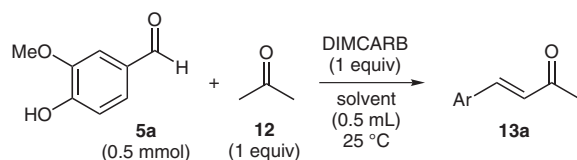
**Scheme 1** Three-step synthesis of shogaols **2** without protecting groups: (a) Mannich-type condensation; (b) reduction; (c) Mannich-type condensation

First, we carefully investigated the Mannich-type condensation of vanillin (**5a**) with acetone (**12**) using DIMCARB (**7**) as shown in Table 1, since only one example of using acetone donor was reported.<sup>5</sup> According to original procedure, the reaction was carried out in DIMCARB as reaction medium and catalyst, furnishing the desired enone **13a** in moderate yield (entry 1). A series of different solvent systems was evaluated. In general, in polar solvents unidentified tailing spots on TLC were observed, while



**Scheme 2** DIMCARB-mediated Mannich-type reaction

**Table 1** Mannich-Type Condensation of Vanillin (**5a**) with Acetone (**12**) Using DIMCARB<sup>a</sup>



| Entry           | Solvent                         | Time (h) | Yield (%) <sup>b</sup> |
|-----------------|---------------------------------|----------|------------------------|
| 1 <sup>c</sup>  | DIMCARB                         | 24       | 41                     |
| 2               | DMSO                            | 24       | 25                     |
| 3               | DMF                             | 24       | 44                     |
| 4               | MeCN                            | 24       | 52                     |
| 5               | 1,4-dioxane                     | 30       | 52                     |
| 6               | Et <sub>2</sub> O               | 6        | 59                     |
| 7               | THF                             | 30       | 62                     |
| 8               | MeOH                            | 24       | 26                     |
| 9               | 2-PrOH                          | 6        | 63                     |
| 10 <sup>d</sup> | acetone                         | 24       | 63                     |
| 11              | hexane                          | 6        | 42                     |
| 12              | toluene                         | 30       | 69                     |
| 13              | CHCl <sub>3</sub>               | 48       | 70                     |
| 14              | CH <sub>2</sub> Cl <sub>2</sub> | 48       | 81                     |

<sup>a</sup> Reactions were carried out using vanillin (**5a**, 0.5 mmol), acetone (**12**, 0.5 mmol), and DIMCARB (**7**, 0.5 mmol) in the solvent (0.5 mL) at 25 °C for 6–48 h, unless otherwise noted.

<sup>b</sup> Isolated yield.

<sup>c</sup> DIMCARB (2.5 equiv) was used.

<sup>d</sup> Acetone (0.5 mL, 14 equiv) was used.

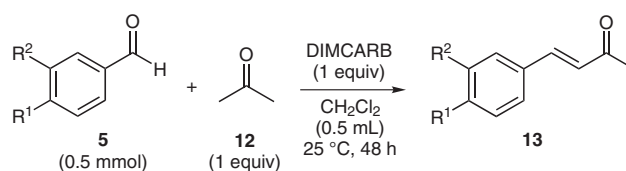
those spots decreased in nonpolar solvents. DMSO, DMF, and acetonitrile were inferior solvents in terms of product yield (entries 2–4). Ethers were moderate solvent (entries 5–7). Methanol is a poor solvent, whereas 2-propanol is a better solvent (entries 8 and 9). Excess acetone donor did not improve the chemical yield (entry 10). Aromatic hydrocarbon solvent, such as toluene, afforded the enone **13a** in 69% yield (entry 12). Halogenated solvent, especially dichloromethane, gave the highest chemical yield without formation of dibenzalacetone derivatives among

solvents tested; therefore, we mainly chose dichloromethane as a solvent for further study (entry 14).<sup>7,8</sup>

The scope of this class of Mannich-type condensations using DIMCARB was examined with a series of aromatic aldehyde acceptors **5**. Results were shown in Table 2. Stabilizing functional groups in formation of the iminium cation intermediate **8** enhanced chemical yields (entries 1–4). On the other hand, destabilizing groups, such as nitro group, gave rise to unidentified products; the desired enone **13f** was obtained in 36% yield (entry 6).

Next, chemoselective reduction of the enone **13a** to zingerone (**3a**) was examined as shown in Table 3. Pd/C-catalyzed hydrogenation of **13a** without additive resulted in the mixture of the desired product **3a** in 88% yield and overhydrogenated alcohol **14a** in 12% yield (entry 1). According to the reported procedure,<sup>3c</sup> with 10 mol% of acetic acid as an additive the alcohol **14a** was still formed in 37% yield (entry 2), although this additive was highly effective in the hydrogenation of the enone **13c** to give raspberry ketone **3c** used in perfumery, in cosmetics, and as flavor (entry 5). Recently, Sajiki and co-workers developed a Pd/C-catalyzed chemoselective hydrogenation using diphenylsulfide as a catalyst poison.<sup>9</sup> The enone **13a** was treated in the presence of 1 mol% diphenylsulfide in ethanol to afford zingerone (**3a**) in 94% yield (entry 3). In spite of the high yield of **3**, using sulfur compounds would be avoided preferably in perfumery, in cosmetics, and as flavor. We found that Lewis base catalyzed conjugate reduction of **13** using trichlorosilane developed by Nakajima and co-workers afforded the desired compounds **3**.<sup>10</sup> The reduction of **13a** with HSiCl<sub>3</sub> was performed in the presence of HMPA (20 mol%), affording zingerone (**3a**) in 87% yield (entry 4). Similarly, raspberry ketone **3c** was obtained in 79% yield (entry 6).

**Table 2** Mannich-Type Condensation of Arylaldehyde **5** with Acetone (**12**) Using DIMCARB<sup>a</sup>

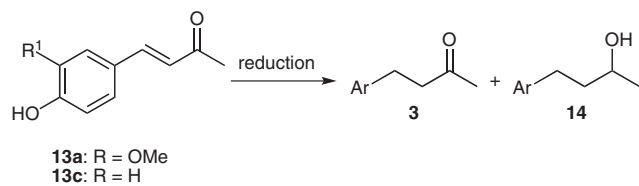


| Entry          | <b>5</b>  | R <sup>1</sup>  | R <sup>2</sup> | Yield (%) <sup>b</sup> | <b>13</b>  |
|----------------|-----------|-----------------|----------------|------------------------|------------|
| 1              | <b>5a</b> | OH              | OMe            | 81                     | <b>13a</b> |
| 2 <sup>c</sup> | <b>5b</b> | OMe             | H              | 75                     | <b>13b</b> |
| 3              | <b>5c</b> | OH              | H              | 58                     | <b>13c</b> |
| 4              | <b>5d</b> | H               | H              | 63                     | <b>13d</b> |
| 5              | <b>5e</b> | Cl              | H              | 76                     | <b>13e</b> |
| 6              | <b>5f</b> | NO <sub>2</sub> | H              | 36                     | <b>13f</b> |

<sup>a</sup> Reactions were carried out using vanillin (**5a**, 0.5 mmol), acetone (**12**, 0.5 mmol), and DIMCARB (**7**, 0.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) at 25 °C for 48 h, unless otherwise noted.

<sup>b</sup> Isolated yield.

<sup>c</sup> The reaction was carried out in acetone (0.5 mL, 14 equiv) instead of CH<sub>2</sub>Cl<sub>2</sub> for 18 h.

**Table 3** Chemoselective Reduction of the Enone **13** to Zingerone Derivatives **3**

| Entry            | <b>13</b>  | Conditions                               | Yield of <b>3</b> (%) | Yield of <b>14</b> (%) |
|------------------|------------|--|-----------------------|------------------------|
| 1 <sup>a</sup>   | <b>13a</b> | Pd/C, H <sub>2</sub>                     | 88                    | 12                     |
| 2 <sup>a,b</sup> | <b>13a</b> | Pd/C, H <sub>2</sub> , AcOH              | 58                    | 37                     |
| 3 <sup>a,c</sup> | <b>13a</b> | Pd/C, H <sub>2</sub> , Ph <sub>2</sub> S | 94                    | 0                      |
| 4 <sup>d</sup>   | <b>13a</b> | HSiCl <sub>3</sub> , HMPA                | 87                    | 0                      |
| 5 <sup>a,b</sup> | <b>13c</b> | Pd/C, H <sub>2</sub> , AcOH              | 99                    | 0                      |
| 6 <sup>d</sup>   | <b>13c</b> | HSiCl <sub>3</sub> , HMPA                | 79                    | 0                      |

<sup>a</sup> Reactions were carried out using Pd/C (10 mol%) and H<sub>2</sub> (balloon) in MeOH for 24 h at r.t.

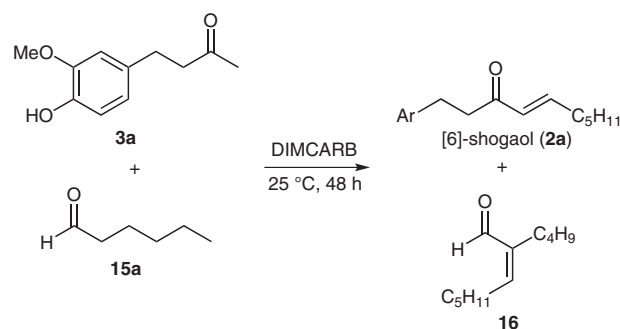
<sup>b</sup> AcOH (10 mol%) was used.

<sup>c</sup> Ph<sub>2</sub>S (1 mol%) was used.

<sup>d</sup> Reactions were carried out using HSiCl<sub>3</sub> (2 equiv) and HMPA (20 mol%) in CH<sub>2</sub>Cl<sub>2</sub> for 2 h at 0 °C.

Next, we examined syntheses of [6]-shogaol (**2a**) as shown in Table 4. There is no report on the DIMCARB-mediated Mannich-type condensation of the aliphatic aldehyde acceptor with the ketone donor previously. Control of the formation of self-Mannich product **16** is very important to prepare the desired shogaol **2a**. Although best reaction conditions in Table 1 were applied to the synthesis of [6]-shogaol **2a**, Z-isomer of self-Mannich product **16** was obtained as a major product (entry 1). Evaluation of various solvents furnished that DIMCARB is the best reaction medium (entry 2); hence, further studies were carried out without addition of conventional organic solvent.<sup>11</sup> Increasing the amount of aldehyde acceptor improved the chemical yield of **2a** up to 74% along with an increase in formation of self-Mannich product **16** (entries 2–5). Keeping low concentration of hexanal acceptor **15a** would be a key to suppressing self-Mannich reaction.<sup>12</sup> Addition of **15a** by use of syringe pump over 10 hours, the desired [6]-shogaol (**2a**) was obtained in 59% yield along with **16** in less than 5% yield (entry 6). Chemical yields were up to 80%, when three equivalents of the acceptor **15a** were used (entries 7–9).<sup>13</sup> The DIMCARB-mediated Mannich-type condensation of the aliphatic aldehyde acceptor **15a** with the ketone donor **3a** for preparing [6]-shogaol (**2a**) was achieved by easy manipulation under mild conditions, that is, just mixing the donor and DIMCARB and slow addition of the acceptor.

The scope of this class of Mannich-type condensations using DIMCARB was examined with a series of aldehyde acceptors. Results were shown in Table 5. With liquid aliphatic aldehyde acceptors **15** Mannich-type condensa-

**Table 4** Mannich-Type Condensation of Hexanal (**15a**) with the Ketone **3a** Using DIMCARB<sup>a</sup>

| Entry          | <b>15a</b> (equiv) | Yield of <b>2a</b> (%) | Yield of <b>16</b> (%) |
|----------------|--------------------|------------------------|------------------------|
| 1 <sup>b</sup> | 1                  | 4                      | 36                     |
| 2              | 1                  | 48                     | 5                      |
| 3              | 2                  | 56                     | 8                      |
| 4              | 3                  | 62                     | 10                     |
| 5              | 10                 | 74                     | 24                     |
| 6 <sup>c</sup> | 1                  | 59                     | <5                     |
| 7 <sup>c</sup> | 1.5                | 65                     | <5                     |
| 8 <sup>c</sup> | 2                  | 77                     | <5                     |
| 9 <sup>c</sup> | 3                  | 80                     | <5                     |

<sup>a</sup> Reactions were carried out using the ketone (**3a**, 0.3 mmol), hexanal (**15a**, 1–10 equiv), and DIMCARB (7, 0.3 mL, 1.47 mmol) at 25 °C for 48 h, unless otherwise noted.

<sup>b</sup> Reaction was carried out in CH<sub>2</sub>Cl<sub>2</sub>.

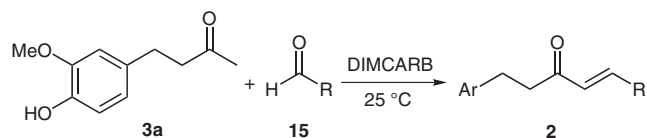
<sup>c</sup> Hexanal (**15a**) was added by use of syringe pump over 10 h.

tions directly afforded desired shogaols **2** in good yields (entries 1–3). It was difficult to add aldehydes with a higher melting point such as nonyl and undecyl aldehydes via syringe pump, however, portionwise addition of them afforded the shogaols **2** in up to 60% and 77% chemical yields, respectively (entries 4 and 5). Reactions with aromatic aldehydes yielded the shogaol derivatives **2** in good yield at 80 °C even when 1.0 equivalent of acceptor was used (entries 6–8), although these reactions did not proceed at 25 °C.

In summary, we have developed the synthesis of shogaols **2** in three steps by use of DIMCARB. Protection and/or deprotection is not required, in addition, waste salts do not generate. All transformations were carried out using metal-free catalysts. Further studies focusing on the full scope of this simple and environmentally friendly synthesis of shogaols **2** are currently under investigation and will be reported in due course.

### Acknowledgment

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**Table 5** Mannich-Type Condensation of the Aldehyde **15** with the Ketone **3a** Using DIMCARB<sup>a</sup>

| Entry          | R                                       | Time (h) | Yield of <b>2</b> (%) |
|----------------|---|----------|-----------------------|
| 1 <sup>b</sup> | Pr                                      | 48       | 70                    |
| 2 <sup>b</sup> | pentyl                                  | 48       | 80                    |
| 3 <sup>b</sup> | heptyl                                  | 48       | 83                    |
| 4 <sup>c</sup> | nonyl                                   | 48       | 60                    |
| 5 <sup>c</sup> | undecyl                                 | 48       | 77                    |
| 6 <sup>d</sup> | 4-HO-3-MeOC <sub>6</sub> H <sub>4</sub> | 8        | 74                    |
| 7 <sup>d</sup> | 4-MeOC <sub>6</sub> H <sub>4</sub>      | 18       | 76                    |
| 8 <sup>d</sup> | Ph                                      | 10       | 76                    |

<sup>a</sup> Reactions were carried out using the ketone (**3a**, 0.3 mmol), aldehydes (**15**, 1–3 equiv), and DIMCARB (7, 0.3 mL, 1.47 mmol) at 25 °C, otherwise noted.

<sup>b</sup> Aldehydes **15** were added by use of syringe pump over 10 h.

<sup>c</sup> Aldehydes **15** were added portionwise (3 × 1 equiv).

<sup>d</sup> Reactions were carried out at 80 °C in CH<sub>2</sub>Cl<sub>2</sub> using DIMCARB (0.5 equiv) in a pressure-resisted tube.

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## (7) Typical Procedure

Handling of this class of reaction is very simple. DIMCARB (**7**, 101 μL, 0.5 mmol) was added to the solution of vanillin (**5a**, 76.1 mg, 0.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) at 25 °C. Gas was evolved. Acetone (**12**, 36.7 μL, 0.5 mmol) was added in a single portion. Stirring was continued for 48 h. The solvent mixture was acidified with 10% HCl aq (2 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 3 mL). The combined organic fraction was dried with anhyd Na<sub>2</sub>SO<sub>4</sub>, filtrated, and solvent removed in vacuo. Purification with column chromatography (silica gel, hexane–EtOAc) gave the enone **13a** (77.8 mg, 81%) as a pale yellow solid. Without extraction, the crude reaction mixture could be directly purified by column chromatography in decreasing to 56% chemical yield.

- (8) We further investigated decreasing amount of DIMCARB, but chemical yields also decreased in the Mannich-type condensation of vanillin (**5a**) with acetone (**12**). Amount of DIMCARB = 1.0 equiv: 81%; 0.5 equiv: 72%; 0.1 equiv: 41%. These results suggested that DIMCARB catalyzed the Mannich-type condensation; however, due to low catalytic ability, a stoichiometric amount of DIMCARB was used for the present reactions.

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- (11) Reactions in conventional solvents such as DMSO, DMF, MeCN, 1,4-dioxane, Et<sub>2</sub>O, THF, MeOH, 2-PrOH, toluene, and CHCl<sub>3</sub> resulted in low chemical yields (**2a**: 0–19%) along with self-Mannich product in 6–42% yields.

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## (13) Typical Procedure

To a solution of the aldehyde (**3a**, 58.9 mg, 0.3 mmol) in DIMCARB (**7**, 300 μL, 1.47 mmol) was added dropwise hexanal (**15a**, 110 μL, 0.9 mmol) by use of syringe pump over 10 h at 25 °C. Stirring was continued for 48 h. The solvent mixture was acidified with 10% HCl aq (2 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 3 mL). The combined organic fraction was dried with anhyd Na<sub>2</sub>SO<sub>4</sub>, filtrated, and solvent removed in vacuo. Purification with column chromatography (silica gel, hexane–EtOAc) gave [6]-shogaol **2a** (66.4 mg, 80%) as a pale yellow liquid; registry number 555-66-8; *R*<sub>f</sub> = 0.51 (hexane–EtOAc = 70:30). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 0.89 (t, *J* = 6.8 Hz, 3 H, CH<sub>3</sub>), 1.15–1.57 (m, 6 H, 3 × CH<sub>2</sub>), 2.10–2.28 (m, 2 H, CH=CHCH<sub>2</sub>), 2.75–2.96 (m, 4 H, CH<sub>2</sub>CH<sub>2</sub>Ar), 3.87 (s, 3 H, OCH<sub>3</sub>), 6.09 (dt, *J* = 15.8, 1.1 Hz, 1 H, COCH=CH), 6.68 (dd, *J* = 7.9, 1.7 Hz, 1 H, H-6), 6.71 (d, *J* = 1.7 Hz, 1 H, H-2), 6.82 (dt, *J* = 15.8, 6.9 Hz, 1 H, COCH=CH), 6.83 (d, *J* = 7.9 Hz, 1 H, H-5). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 200.01 (C), 147.95 (CH), 146.49 (C), 143.95 (C), 133.19 (C), 130.29 (CH), 120.77 (CH), 114.35 (CH), 111.16 (CH), 55.74 (OCH<sub>3</sub>), 41.80 (CH<sub>2</sub>), 32.26 (CH<sub>2</sub>), 31.16 (CH<sub>2</sub>), 29.72 (CH<sub>2</sub>), 27.58 (CH<sub>2</sub>), 22.22 (CH<sub>2</sub>), 13.72 (CH<sub>3</sub>). GC (TD-17, T<sub>inj</sub> = 250 °C, T<sub>det</sub> = 250 °C, He = 0.5 kg/cm<sup>2</sup>, H<sub>2</sub> = 0.5 kg/cm<sup>2</sup>, air = 0.5 kg/cm<sup>2</sup>, T<sub>i</sub> = 250 °C): t<sub>R</sub> = 9.410 min; HPLC [Mightysil, hexane–2-PrOH (95:5), flow rate 1.0 mL/min, λ = 254 nm]: t<sub>R</sub> = 13.575 min.

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