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# Alkyl and Aryl 4,5-Dichloro-6-oxopyridazin-1(6*H*)-carboxylates: A Practical Alternative to Chloroformates for the Synthesis of Symmetric and Asymmetric Carbonates

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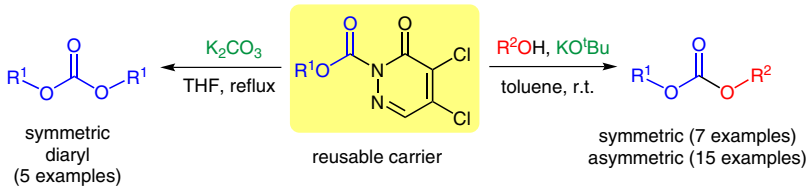


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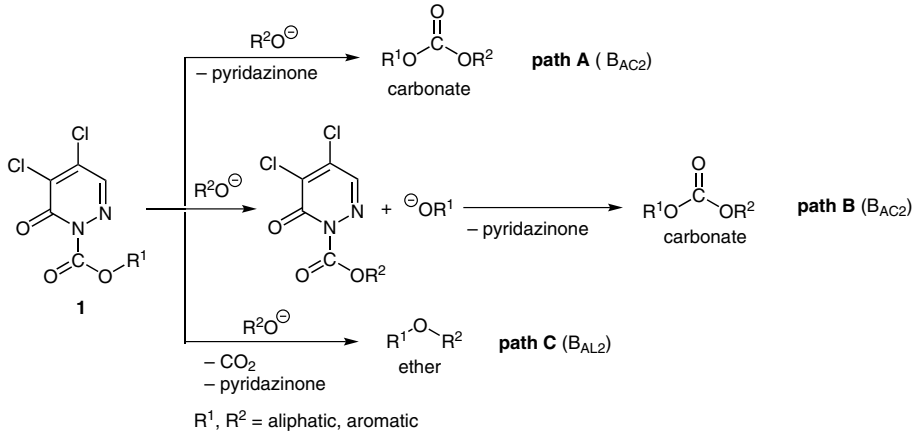
**Abstract** Symmetric and asymmetric carbonates were synthesized by using alkyl or aryl 4,5-dichloro-6-oxopyridazin-1(6*H*)-carboxylates. Five aryl 4,5-dichloro-6-oxopyridazin-1(6*H*)-carboxylates were converted into the corresponding diaryl carbonates in good to excellent yields by treatment with potassium carbonate in refluxing THF. When the 4,5-dichloro-6-oxopyridazin-1(6*H*)-carboxylates were treated with aliphatic or aromatic alcohols in the presence of potassium *tert*-butoxide in toluene at room temperature, they gave the corresponding symmetric or asymmetric carbonates in moderate to excellent yields. Alkyl and aryl 4,5-dichloro-6-oxopyridazin-1(6*H*)-carboxylates are therefore efficient, stable, and ecofriendly alternatives to chloroformates.

**Key words** pyridazines, alcohols, phenols, carbonates, alkoxycarbonylations, acyl-transfer agents

Alkyl and aryl chloroformates ClC(=O)OR are important sources of alkoxy- or aryloxycarbonyl moieties for a wide number of synthetic applications.[2] A common use of chloroformates is in the synthesis of carbonates.[3] However, acyl-transfer reactions with chloroformates have several disadvantages; for example, chloroformate derivatives are usually sensitive to moisture, they are gaseous substances under ambient conditions, and they generate hydrochloric acid as a toxic and strongly acidic byproduct of the reaction. Here, we report new types of heterocycle-based reagents, the *N*-(alkoxycarbonyl)- and *N*-(aryloxycarbonyl)azinones, which might serve as alternatives to chloroformates for preparing symmetric or asymmetric carbonates without the disadvantages discussed above. Reactions of *N*-(alkoxycarbonyl)- or *N*-(aryloxycarbonyl)azinones with various acyl moieties under basic conditions ($K_2CO_3$ or *t*-BuOK) gave asymmetric and symmetric carbonates in moderate to excellent yields (Scheme 1).

Previous studies[4] established that pyridazin-3(2*H*)-ones are attractive functional-group carriers. They readily form stable anionic structures and thereby act as good leaving groups; furthermore, they are inexpensive, stable (insensitive to air or moisture), easy to synthesize, easily remov-

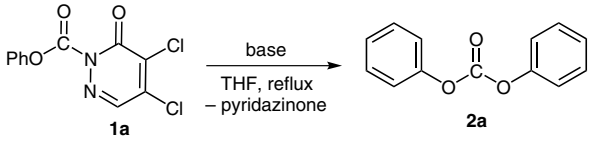



**Scheme 1** Reaction pathways under basic conditions for alkyl or aryl 4,5-dichloro-6-oxopyridazin-1(6*H*)-carboxylates **1**

able, and recyclable. These features make alkyl or aryl 4,5-dichloro-6-oxopyridazin-1(6*H*)-carboxylates **1** (Scheme 1) practical and efficient sources of alkoxy- or aryloxycarbonyl moieties. Using these heterocycle-based acyl-group carriers, we wished to develop a synthetic method for preparing symmetric or asymmetric carbonates. Scheme 1 shows possible reaction routes for synthesizing carbonates with compounds **1**; reactions of pyridazines **1** with alcohols under basic conditions might give the corresponding carbonates by $B_{AC2}$ reactions (paths A and B, respectively), together with ethers, formed as byproducts by a $B_{AL2}$ reaction (path C).[5]

To identify the optimal reaction conditions, we first attempted to prepare structurally simple symmetric diphenyl carbonate (**2a**) by homocoupling of phenyl 4,5-dichloro-6-oxopyridazine-1(6*H*)-carboxylate (**1a**)[4a] in the presence of various bases in refluxing THF (Table 1). The reaction of **1a** in the absence of a base in refluxing THF did not give the product **2a** (Table 1, entry 11), whereas the reaction of **1a** in the presence of an inorganic or organic base (except for DMAP) gave carbonate **2a** in 19–98% yield (entries 1–10). Among the seven bases investigated, potassium carbonate gave the best results (entries 1–3). We did not detect the diphenyl ether byproduct, potentially formed through path C in Scheme 1.

**Table 1** Screening of Bases for the Synthesis of Carbonate **2a** from Pyridazine **1a** in Refluxing THF[a]



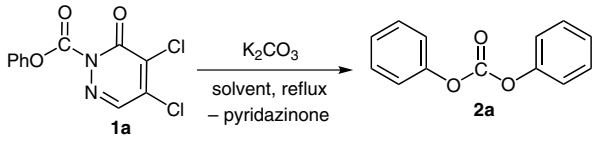

**1a** **2a**

| Entry | Base (equiv) | Time (h) | Yield[b] of **2a** (%) |
|---|---|---|---|
| 1 | $K_2CO_3$ (2) | 2 | 98 |
| 2 | $K_2CO_3$ (1) | 2 | 98 |
| 3 | $K_2CO_3$ (0.5) | 2 | 98 |
| 4 | $K_2CO_3$ (0.25) | 2 | 44 |
| 5 | *t*-BuOK (1) | 3 | 76 |
| 6 | NaOMe (1) | 3 | 89 |
| 7 | NaOH (1) | 3 | 19[c] |
| 8 | KOH (1) | 3 | 20[c] |
| 9 | DMAP (1) | 3 | trace |
| 10 | $Et_3N$ (1) | 3 | 64[c] |
| 11 | – | 3 | NR |

[a] Reaction conditions: **1a** (1 equiv), base (0.25–2 equiv), THF, reflux.
[b] Isolated yield; NR = no reaction.
[c] Unidentified products were detected by TLC.

After optimizing the stoichiometry of potassium carbonate (entries 1–4) and screening reaction solvents (Table 2), the optimum reaction conditions were determined to be compound **1a** (1 equiv), $K_2CO_3$ (0.5 equiv), THF, reflux.

**Table 2** Screening of Solvents for the Synthesis of Carbonate **2a** from Pyridazine **1a** in the Presence of $K_2CO_3$ in Refluxing Solvent[a]



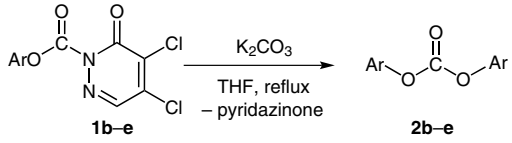

**1a** **2a**

| Entry | Solvent | Time (h) | Yield[b] of **2a** (%) |
|---|---|---|---|
| 1 | THF | 2 | 98 |
| 2 | hexane | 3 | NR |
| 3 | $CH_2Cl_2$ | 3 | trace |
| 4 | toluene | 3 | trace |
| 5 | EtOAc | 3 | 34[c] |
| 6 | MeCN | 3 | 41[c] |

[a] Reaction conditions: mole ratio of **1a**/$K_2CO_3$ = 1:0.5.
[b] Isolated yields; NR = no reaction.
[c] Compound **1a** was recovered.

Next, we examined the substrate scope for the synthesis of symmetric aryl carbonates through reactions of aryl 4,5-dichloro-6-oxopyridazine-1(6*H*)-carboxylates with various substituents (Table 3; **1b**–**e**) under the optimized reaction conditions. The corresponding symmetric carbonates **2b**–**e** were obtained in good to excellent yields (80–97%). However, treatment of alkyl 4,5-dichloro-6-oxopyridazine-1(6*H*)-carboxylates **1** with $K_2CO_3$ or alkoxides (NaOMe or *t*-BuOK) under the same conditions did not produce the corresponding dialkyl carbonates. For the synthesis of diaryl carbonates, only half a mole of $K_2CO_3$ relative to **1a** was required. This finding indicates that the reaction is assisted by potassium carbonate.

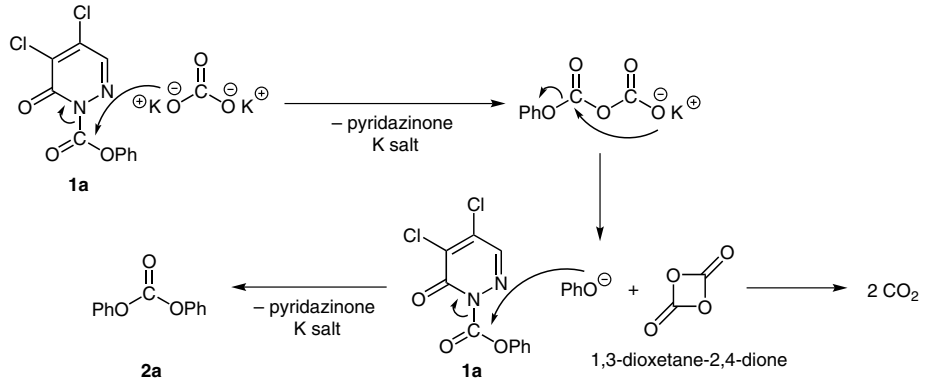
**Table 3** Synthesis of Diaryl Carbonates **2b**–**e** by the $K_2CO_3$-Assisted Reaction of **1** in Refluxing THF[a]




**1b–e** **2b–e**

| Entry | Ar | Time (h) | Product | Yield[b] (%) |
|---|---|---|---|---|
| 1 | 4-$ClC_6H_4$ | 1 | **2b** | 97 |
| 2 | 4-$O_2NC_6H_4$ | 18 | **2c** | 87 |
| 3 | 4-Tol | 10 | **2d** | 80 |
| 4 | 4-$MeOC_6H_4$ | 7 | **2e** | 84 |

[a] Reaction conditions: mole ratio of **1a**/$K_2CO_3$ = 1:0.5.
[b] Isolated yields.




**Scheme 2** Plausible mechanism for the synthesis of **2a** by the $K_2CO_3$-assisted reaction of compound **1a**

A plausible mechanism that addresses the role of $K_2CO_3$ in the reaction is proposed in Scheme 2.

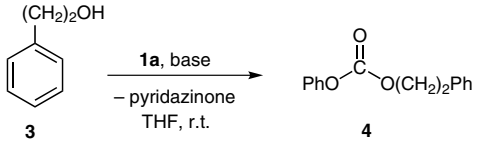
We then attempted to prepare asymmetric carbonates through the reaction of pyridazine **1a** with various alcohols under the reaction conditions optimized for the symmetric carbonates. A test reaction of one equivalent of **1a** with one equivalent of 2-phenylethanol (**3**) in the presence of $K_2CO_3$ (0.5 equiv) in refluxing THF gave diphenyl carbonate (**2a**) as the major product, together with a trace amount of phenyl 2-phenylethyl carbonate (**4**), the desired product (Scheme 3).

We therefore screened various bases and solvents to optimize the reaction conditions for the synthesis of asymmetric carbonates. Among the six bases ($K_2CO_3$, *t*-BuOK, NaOMe, NaOH, KOH, and DMAP) that were tested in THF at room temperature (Table 4), the best result [65% yield of phenyl 2-phenylethyl carbonate (**4**)] was obtained when one equivalent of *t*-BuOK was used as the base (Table 4, entry 2).

Among the seven solvents that were screened for the reaction of alcohols with **1a** in the presence of *t*-BuOK at room temperature, toluene gave the best results (Table 5, entry 1). Based on these preliminary experiments, we determined that the optimal reaction conditions for the synthesis of asymmetric carbonates were alcohol (1 equiv), **1a** (1 equiv), *t*-BuOK (1 equiv), toluene, room temperature.

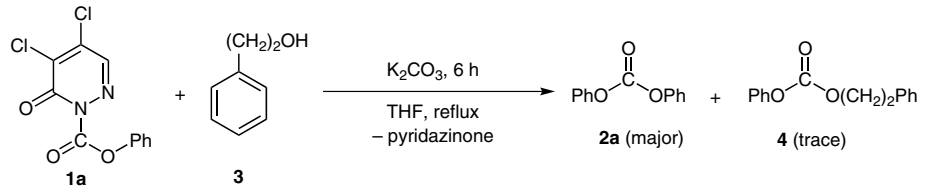
To examine the substrate scope for the synthesis of asymmetric carbonates, we studied the reactions of alcohols **5** with aryl or alkyl 4,5-dichloro-6-oxopyridazin-1(6*H*)-carboxylates (**1a** and **1f**, respectively) in the presence of *t*-BuOK in toluene at room temperature (Table 6). The reaction of various aliphatic and aromatic alcohols **5** with ethyl 4,5-dichloro-6-oxopyridazine-1(6*H*)-carboxylate (**1f**) gave the corresponding asymmetric carbonates **6a**–**g** in 67–90% yields (Table 6, entries 1–7). The corresponding reaction of aliphatic and aromatic alcohols **5** with phenyl 4,5-

**Table 4** Screening of Bases for the Synthesis of Asymmetric Carbonate **4** by the Reaction of Alcohol **3** with Pyridazine **1a** in THF at Room Temperature[a]



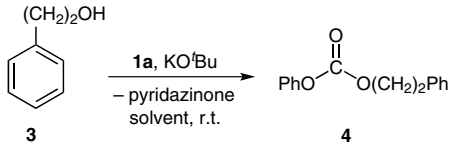

| Entry | Base | Time (h) | Yield[b] of **4** (%) |
|---|---|---|---|
| 1 | $K_2CO_3$ | 6 | trace[c] |
| 2 | *t*-BuOK | 0.5 | 65 |
| 3 | NaOMe | 6 | NR |
| 4 | NaOH | 6 | NR |
| 5 | KOH | 6 | NR |
| 6 | DMAP | 6 | trace |

[a] Reaction conditions: base (1 equiv); mole ratio **3**/**1a**/base = 1:1:1.
[b] Isolated yield; NR = no reaction.
[c] $(PhO)_2CO$ (**2a**) was detected instead of **4**.




**Scheme 3** Reaction of pyridazine **1a** with 2-phenylethanol (**3**) in the presence of $K_2CO_3$ in refluxing THF

**Table 5** Screening of Solvents for the Synthesis of Asymmetric Carbonate **4** by the Reaction of 2-Phenylethanol (**3**) with Pyridazine **1a** in the Presence of *t*-BuOK at Room Temperature[a]




**3** **4**

| Entry | Solvent | Time (h) | Yield[b] of **4** (%) |
|---|---|---|---|
| 1 | toluene | 0.5 | 87 |
| 2 | hexane | 8 | 9 |
| 3 | $CH_2Cl_2$ | 8 | 15 |
| 4 | THF | 0.5 | 65 |
| 5 | EtOAc | 8 | 19 |
| 6 | $Et_2O$ | 8 | 46 |
| 7 | DMSO | 1 | 34 |

[a] Reaction conditions: mole ratio **5**/**1a**/*t*-BuOK = 1:1:1.
[b] Isolated yields.

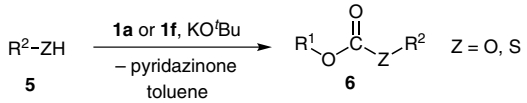
dichloro-6-oxopyridazine-1(6*H*)-carboxylate (**1a**) under the optimized conditions afforded the corresponding asymmetric carbonates **6h**–**n** in 58–94% yield (entries 8–14). No significant trend in substituent effects of the aromatic alcohols was observed. The reaction of pyridazine **1a** with benzenethiol gave *O*,*S*-diphenyl thiocarbonate (**6o**) in 85% yield (entry 15).

We also determined whether the reaction conditions used for synthesizing asymmetric carbonates could be applied in the synthesis of symmetric carbonates. The reaction of aliphatic or aromatic alcohols **5** with the appropriate pyridazines **1a**–**g** in the presence of *t*-BuOK in toluene at room temperature gave the corresponding symmetric carbonates **2a**–**g** in 45–89% yields (Table 7).

The structures of the synthesized carbonates were established by $^1H$ and $^{13}C$ NMR, HRMS, and FTIR spectroscopy (see the Supporting Information). In all experiments, 4,5-dichloropyridazin-3(2*H*)-one was isolated quantitatively and reused.

In summary, we have demonstrated the versatility of alkyl and aryl 4,5-dichloro-6-oxopyridazin-1(6*H*)-carboxylates in the synthesis of symmetric and asymmetric carbonates. The reactions were facilitated by bases such as $K_2CO_3$ or *t*-BuOK. The reactions of aryl 4,5-dichloro-6-oxopyridazin-1(6*H*)-carboxylates in the presence of $K_2CO_3$ in refluxing THF gave symmetric carbonates in good to excellent yields. The reactions of alkyl and aryl 4,5-dichloro-6-oxopyridazin-1(6*H*)-carboxylates with aliphatic or aromatic alcohols in the presence of *t*-BuOK (a greener alternative product, according to Sigma-Aldrich)[6] in toluene at room temperature gave the corresponding symmetric or asymmetric carbonates in moderate to excellent yields.

**Table 6** Synthesis of Asymmetric Carbonates **6** by the Reaction of Alcohols **5** with Pyridazines **1a** or **1f** in the Presence of *t*-BuOK in Toluene at Room Temperature[a]

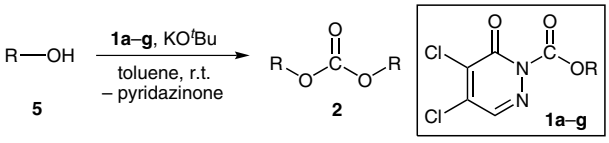



**5** **6**

| Entry | $R^1$ | $R^2$ | Time (h) | Product | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | Et | Bu | 1 | **6a** | 84 |
| 2 | Et | Cy | 2 | **6b** | 78 |
| 3 | Et | $(CH_2)_2Ph$ | 1 | **6c** | 67 |
| 4 | Et | 4-$ClC_6H_4$ | 0.5 | **6d** | 76 |
| 5 | Et | 4-$MeOC_6H_4$ | 0.3 | **6e** | 90 |
| 6 | Et | 4-$O_2NC_6H_4$ | 0.2 | **6f** | 86 |
| 7 | Et | 4-$PhC_6H_4$ | 1 | **6g** | 86 |
| 8 | Ph | Me | 1 | **6h** | 58 |
| 9 | Ph | Bu | 3 | **6i** | 71 |
| 10 | Ph | Cy | 6 | **6j** | 77 |
| 11 | Ph | 4-$ClC_6H_4$ | 0.5 | **6k** | 94 |
| 12 | Ph | 4-$MeOC_6H_4$ | 2 | **6l** | 72 |
| 13 | Ph | 4-$O_2NC_6H_4$ | 0.5 | **6m** | 94 |
| 14 | Ph | 4-$PhC_6H_4$ | 1 | **6n** | 77 |
| 15 | Ph | Ph[c] | 0.5 | **6o** | 85 |

[a] Reaction conditions: mole ratio of **7**/**1**/*t*-BuOK = 1:1:1.
[b] Isolated yields.
[c] The starting material was PhSH instead of PhOH.

**Table 7** Synthesis of the Symmetric Carbonates **2** by the Reaction of Alcohols **5** with Pyridazines **1** in the Presence of *t*-BuOK in Toluene at Room Temperature[a]




**5** **2**

| Entry | R | Time (min) | Product | Yield[b] (%) |
|---|---|---|---|---|
| 1 | Ph | 15 | **2a** | 80 |
| 2 | 4-$ClC_6H_4$ | 15 | **2b** | 79 |
| 3 | 4-$O_2NC_6H_4$ | 15 | **2c** | 74 |
| 4 | 4-Tol | 20 | **2d** | 74 |
| 5 | 4-$MeOC_6H_4$ | 15 | **2e** | 89 |
| 6 | Et | 10 | **2f** | 81[c] |
| 7 | Me | 20 | **2g** | 45[c] |

[a] Reaction conditions: mole ratio of **5**/**1**/*t*-BuOK = 1:1:1.
[b] Isolated yield.
[c] The reaction was carried out in the corresponding alcohol as solvent.

The reaction method described in this work permits efficient, convenient, and ecofriendly preparation of symmetric and asymmetric carbonates. This method takes advantage of alkyl and aryl 4,5-dichloro-6-oxopyridazin-1(6*H*)-carboxylates, which are readily synthesized and derived from quantitatively isolable and recyclable 4,5-dichloropyridazin-3(2*H*)-one.[4a,d,e,7] We believe that the method reported here[8] will find a broad range of applications for alkoxy- and aryloxycarbonyl sources in flow and ecofriendly synthetic chemistry.

## Acknowledgment

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## Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561411.

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(1) These authors contributed equally to this work.
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(8) **Symmetric Carbonates 2a–e; General Procedure Using Potassium Carbonate**
$K_2CO_3$ (1.0 mmol) was added to a solution of the appropriate pyridazine **1** (1.0 mmol) in THF (20 mL), and the mixture was allowed to reflux until pyridazine **1** was consumed (TLC). The solvent was evaporated under reduced pressure, and the symmetric carbonates **2a–e** were isolated by column chromatography [silica gel (2.5 × 3 cm), $CH_2Cl_2$]. Once the desired product had been isolated, the column was eluted with EtOAc to isolate 4,5-dichloropyridazin-3(2*H*)-one, which was obtained quantitatively and reused.
**Diphenyl Carbonate** (**2**)
White solid; yield: 193 mg (80%); mp 75–76 °C. IR (KBr): 3058, 1773, 1592, 1490, 1255, 1233, 1182, 1071, 1016, 996, 751, 685, 501 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ = 7.30–7.35 (m, 2 H), 7.40–7.51 (m, 8 H). $^{13}C$ NMR (75 MHz, DMSO-$d_6$): δ = 121.2, 126.4, 129.7, 150.7, 151.7. HRMS (EI): *m/z* [$M^+$] calcd for $C_{13}H_{10}O_3$: 214.0630; found: 214.0634.
**Symmetric (2) or Asymmetric (4 and 6) Carbonates; General Procedure Using Potassium *tert*-Butoxide**
Alcohol **3** or **5** (0.84 mmol) was added to a solution of the appropriate pyridazine **1** (0.7 mmol) and *t*-BuOK (0.84 mmol) in toluene (10 mL), and the mixture was stirred at r.t. until pyridazine **1** was consumed (TLC). 10% aq NaOH (50 mL) and $CH_2Cl_2$ (30 mL) were added to the mixture with stirring. The organic layer was separated, washed with $H_2O$ (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was transferred to an open-bed column of silica gel (2.5 × 4 cm), which was eluted with hexane–EtOAc (3:1) to give the symmetric carbonates **2**, or the asymmetric carbonates **4** or **6**, and then eluted with EtOAc to isolate 4,5-dichloropyridazin-3(2*H*)-one quantitatively for reuse.
**Phenyl 2-Phenylethyl Carbonate** (**4**)
White solid; yield: 148 mg (87%); mp 83–85 °C. IR (KBr): 3109, 3081, 3058, 3033, 2969, 2938, 2895, 2868, 1753, 1492, 1260, 1210, 1077, 967, 778, 753, 699, 499 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 3.00 (t, *J* = 7.0 Hz, 2 H), 4.38–4.43 (m, 2 H), 7.10–7.35 (m, 10 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 35.1, 69.1, 121.0, 121.2, 126.1, 126.4, 126.9, 128.7, 129.1, 129.6, 129.7, 137.1, 151.1, 151.2, 153.7. HRMS (EI): *m/z* [$M^+$] calcd for $C_{15}H_{14}O_3$: 242.0943; found: 242.0941.