Pergamon

*Tetrahedron*, Vol. 53, No. 7, pp. 2415-2420, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(96)01187-8

# Facile Preparation of Thiocarbonylimidazolide by Organic Solid State Reaction[1]

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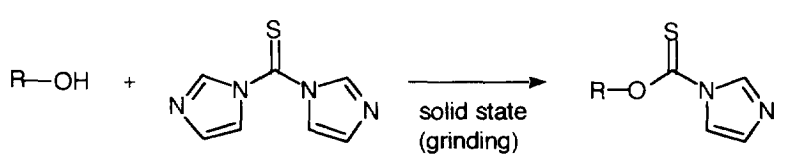
***Abstract***: Thiocarbonylimidazolide **3** has been prepared from alcohol **1** and thiocarbonyldiimidazole **2** by grinding both substrates with pestle and mortar. 

During these two decades there has been explosive expansion in the new area of radical reactions in synthetic organic chemistry.[3] Halides, xanthates or thiocarbonylimidazolides **3** have been employed often as substrates for radical reactions. Among such substrates, thiocarbonylimidazolide **3** is the best choice for natural product syntheses because **3** can be prepared from alcohol **1** and thiocarbonyldiimidazole **2** under neutral reaction conditions where a wide variety of functional groups can survive. However, preparation of thiocarbonylimidazolide **3** by conventional solution chemistry has some drawbacks; in particular, preparation from secondary cyclic alcohols has frequently required longer reaction time at elevated temperature,[4] a large excess of thiocarbonyldiimidazole **2** or even *N,N*-dimethylaminopyridine as an activator under inert atmosphere in a sealed tube.[5] During the course of our synthetic study of a potent inhibitor of HMG-CoA reductase,[6] we encountered the same difficulty, recovering the starting material often even under forced reaction conditions.

We delineate herein a new and facile procedure for preparation of thiocarbonylimidazolide **3** by organic solid state reaction (Scheme 1).[7]




**1** **2** **3**

**Scheme 1**

The present solid state reaction was carried out simply by grinding alcohol **1** and thiocarbonyldiimidazole **2** with pestle and mortar at room temperature in ambient atmosphere. Progress of the reaction was monitored by TLC and the reaction mixture was directly purified by medium pressure liquid chromatography without aqueous workup. Some representative examples are listed in Table 1. Primary and secondary alcohols and a phenol afforded the corresponding thiocarbonylimidazolides **3** in satisfactory yields. Not only crystalline alcohols but also oily alcohols provided thiocarbonylimidazolide **3** as shown in entry 1. Tertiary alcohol such as 1-adamantanol or linalool was recovered intact. A certain amount of the starting material was recovered unchanged in entries 5, 6 and 11, probably due to steric hindrance around the hydroxyl group. The present mild reaction conditions enabled synthesis of the thiocarbonylimidazolide **3j** in satisfactory yield, although our efforts to synthesize the corresponding xanthate ester with sodium hydride or butyllithium, carbon disulfide and iodomethane resulted in decomposition of the starting material.

Grinding both substrates, alcohol **1** and thiocarbonyldiimidazole **2**, with pestle and mortar was essential to get satisfactory results. Simply stirring both crystalline substrates magnetically or ultrasound irradiation in entry 10 did not accelerate the reaction. The yield of **3i** in entry 9 was reduced by high pressure experiment at 8 Kba. These results indicate that the close contact of the two substrates **1** and **2** in high concentration is essential to promote the reaction. Incidentally, yield of **3k** was not improved by addition of *N,N'*-dimethylaminopyridine in entry 11.

In summary, we have shown that the thiocarbonylimidazolides **3** were prepared simply by grinding alcohols **1** and thiocarbonyldiimidazole **2** with pestle and mortar at room temperature in ambient atmosphere. The milder reaction conditions give wider applicability of the present reaction especially for total synthesis of multifunctional natural products. Moreover, efficiency as well as simplicity of operation of the present method will be useful for preparative scale preparation of thiocarbonylimidazolide **3**.

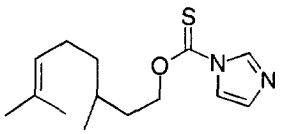
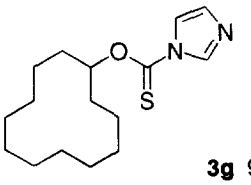
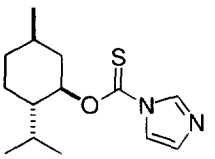
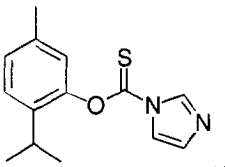
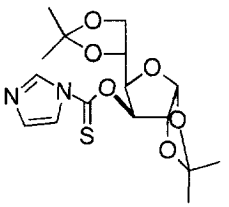
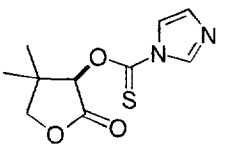
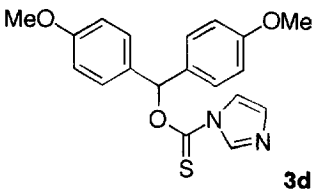
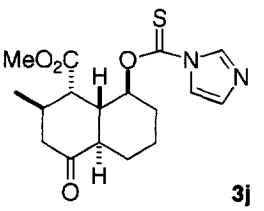
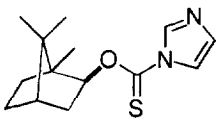
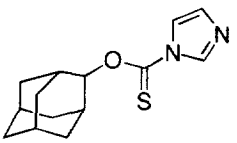
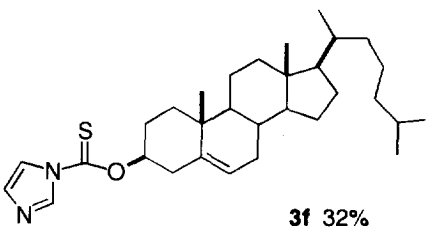
**Acknowledgment**

We thank Prof. N. Katagiri, Pharmaceutical Institute, Tohoku University, for high pressure experiments.

**Experimental**

All m.p.s were determined with a Mitamura Riken hot-stage apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-8300 spectrophotometer for solutions in carbon tetrachloride unless otherwise indicated. $^1$H NMR spectra were obtained for solutions in deuteriochloroform with Bruker MSL-300 (300 MHz) instrument with tetramethylsilane as internal standard. *J*-Values are given in Hz. Mass spectra were run on a JEOL JMS-DX300 spectrometer with a JMA-3500 data system. Medium-pressure liquid chromatography were carried out on a JASCO PRC-50 instrument with a silica gel packed column. Microanalyses were carried out in the microanalytical laboratory of this Institute.

Table 1. Synthesis of Thiocarbonylimidazolide **3**.

| Entry | | Entry | |
|---|---|---|---|
| 1 |  **3a** 91% | 7 |  **3g** 93% |
| 2 |  **3b** 88% | 8 |  **3h** 99% |
| 3 |  **3c** 89% | 9 |  **3i** 94% |
| 4 |  **3d** 85% | 10 |  **3j** 81% |
| 5 |  **3e** 56% | 11 |  **3k** 18% |
| 6 |  **3f** 32% | | |

*General procedure for preparation of thiocarbonylimidazolide* **3**. — A mixture of alcohol **1** and 1.2 equiv. of thiocarbonylimidazole **2** in a mortar was ground well with a pestle at room temperature in ambient atmosphere. Progress of the reaction was monitored by TLC using a glass capillary tube which kept ethanol inside beforehand. In some cases, termination of the reaction was indicated by liquefaction of solid. After grinding occasionally for 2~3hr, the resulting mixture was dissolved in ethyl acetate. The solution was passed through a short column of silica gel. Evaporation of the solvent followed by purification of the residue by medium pressure liquid chromatography provided thiocarbonylimidazolide **3**.

*Citronellyl 1-thiocarbonylimidazolide* **3a**. — Yield, 91%; viscous oil; $\nu_{max}/cm^{-1}$ 2969, 1465, 1386, 1332, 1288, 1233, 1211 and 669;$\delta$ 0.98 (d, 3H, *J* 6 Hz), 1.27 (m, 1H), 1.39 (m, 1H), 1.61 (s, 3H), 1.69 (s, 3H), 1.6 – 1.75 (m, 1H), 2.85 – 2.1 (m, 4H), 4.7 (m, 2H), 5.09 (narrow t, 1H), 7.04 (1H, s), 7.63 (s, 1H) and 8.34 (s, 1H) ; *m/z* 267 ($M^+$ + 1, 0.8%), 266 ($M^+$, 0.8), 138, (55), 123 (34), 95 (45), 83 (32), 82 (42), 81 (53), 69 (100), 55 (42) and 41 (66) (Anal. Calc. for $C_{14}H_{22}ON_2S$: C, 64.12; H, 8.32; N, 10.52. Found: C, 63.27; H, 8.2; N, 10.47).

*Menthyl 1-thiocarbonylimidazolide* **3b**. — Yield, 88%; oil; $\nu_{max}/cm^{-1}$ 2962, 1465, 1333, 1286, 1252 and 1236;$\delta$ 0.82 (d, 3H, *J* 6.8 Hz), 0.93 (d, 3H, *J* 6.8 Hz), 0.96 (d, 3H, *J* 5.9 Hz), 1.0 – 2.4 (m, 9H), 5.43 (td, 1H, *J* 10.5, 5.4 Hz), 7.03 (s, 1H), 7.63 (narrow t, 1H) and 8.33 (s, 1H); *m/z* 138 (30%), 129 (19), 97 (16), 83 (91), 81 (33), 69 (73), 68 (46), 67 (25), 57 (42), 55 (100) and 43 (48) (Anal. Calc. for $C_{14}H_{22}ON_2S$: C, 63.12; H, 8.32; N, 10.52. Found: C, 63.26; H, 8.34; N, 10.44).

*1,2;5,6-Di-O-isopropylidene-3-O-(imidazol-1-ylthiocarbonyl)-α-D-glucofuranoside* **3c**. — Yield, 89%; oil; $\nu_{max}/cm^{-1}$ 2992, 1464, 1391, 1337, 1285, 1238, 1164, 1076 and 1023;$\delta$ 1.29 (s, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 1.57 (s, 3H), 4.1 (m, 2H), 4.16 (m, 2H), 4.76 (d, 1H, *J* 3.1 Hz), 5.82 (d, 1H, *J* 2.2 Hz), 5.95 (d, 1H, *J* 3.7 Hz), 7.07 (s, 1H), 7.61 (s, 1H) and 8.32 (s, 1H); *m/z* 355 (30%), 113 (10), 111 (11), 101 (91), 100 (10), 95 (145), 85 (11), 84 (11), 81 (12), 73 (15), 69 (50), 68 (15), 59 (27), 55 (11) and 43 (100) (Anal. Calc. for $C_{16}H_{22}O_6N_2S$: C, 51.88; H, 5.99; N, 7.56. Found: C, 51.66; H, 5.97; N, 7.37).

*Bis(4-methoxyphenyl)carbinyl 1-thiocarbonylimidazolide* **3d**. — Yield, 85%; m.p. 103~104 °C; $\nu_{max}/cm^{-1}$ 3008, 1697, 1510, 1471, 1364, 1303, 1273, 1251, 1227 and 1176;$\delta$ 3.76 (s, 6H), 6.05 (s, 1H), 6.83 (d, A part of ABtype q, 2H, *J* 9 Hz), 7.06 (s, 1H), 7.29 (d, B part of AB type q, 2H, *J* 9 Hz), 7.43 (s, 1H) and 8.15 (s, 1H); *m/z* 354 ($M^+$, 0.4%), 228 (22), 227 (100), 162 (16), 120 (14), 114 (13), 95 (13), 68 (59), 60 (14) and 41 (18) (Anal. Calc. for $C_{19}H_{18}O_3N_2S$: C, 64.39; H, 5.12; N, 7.9. Found: C, 64.58; H, 5.18; N, 7.72).

*Isobornyl 1-thiocarbonylimidazolide* **3e**. — Yield, 56%; viscous oil; $\nu_{max}/cm^{-1}$ 2961, 1464, 1383, 1340, 1285, 1250, 1235, 1099, 1038 and 970;$\delta$ 0.92 (s, 3H), 0.98 (s, 3H), 1.05 (s, 3H), 1.0 – 2.2 (m, 7H), 5.3 (m, 1H), 7.04 (narrow m, 1H), 7.6 (narrow m, 1H) and 8.3 (s, 1H); *m/z* 265 ($M^+$ + 1, 1%), 264 ($M^+$, 1), 137 (83), 95 (36), 81 (100), 69 (45), 67 (32), 41 (33); Anal. Calc. for $C_{14}H_{20}ON_2S$: C, 63.6; H, 7.62; N, 10.6. Found: C, 63.76; H, 7.52; N, 10.93.

*Cholesteryl 1-thiocarbonylimidazolide* **3f**. — Yield, 32% [cholesterol (62%) was recovered]; m.p. 135~136 °C; $\nu_{max}/cm^{-1}$ 2952, 1466, 1385, 1332, 1287, 1214, 1211 and 981;δ 0.69 (s, 3H), 0.87 (d, 6H, *J* 6.5 Hz), 0.9 – 1.6 (m, 20H), 0.92 (d, 3H, *J* 6.4 Hz), 1.08 (s, 3H), 1.65 – 2.2 (m, 6H), 2.6 (m, 2H), 5.33 (m, 1H), 5.46 (d, 1H, *J* 4.8 Hz), 7.03 (s, 1H), 7.64 (s, 1H) and 8.34 (s, 1H); *m/z* 370 (53%), 369 (100), 147 (37), 95 (38), 69 (37), 57 (37), 55 (39), 43 (48) and 41 (37) (Anal. Calc. for $C_{31}H_{48}ON_2S$: C, 74.95; H, 9.74; N, 5.64. Found: C, 80.25; H, 10.37; N, 5.58).

*Cyclodecyl 1-thiocarbonylimidazolide* **3g**. — Yield, 93%; m.p. 88~89 °C; $\nu_{max}/cm^{-1}$ 2938, 1470, 1384, 1347, 1332, 1285, 1253, 1238 and 980;δ 1.3 – 1.6 (m, 18H), 1.7 (m, 2H), 1.9 (m, 2H), 5.7 (m, 1H), 7.02 (s, 1H), 7.63 (s, 1H) and 8.33 (s, 1H); *m/z* 295 ($M^+$ + 1, 7), 294 ($M^+$, 14%), 129 (67), 97 (40), 83 (51), 69 (100), 68 (69), 55 (91), 43 (40) and 41 (80) (Anal. Calc. for $C_{16}H_{26}ON_2S$: C, 65.27; H, 8.9; N, 9.51. Found: C, 65.28; H, 9.05; N, 9.08).

*Thymoyl 1-thiocarbonylimidazolide* **3h**. — Yield, 99%; viscous oil; $\nu_{max}/cm^{-1}$ 2969, 1465, 1391, 1331, 1290, 1248, 1231, 1201, 1103, 1039 and 967;δ 1.21 (d, 6H, *J* 6.8 Hz), 2.36 (s, 3H), 2.93 (septet, 1H, *J* 6.9 Hz), 6.88 (s, 1H), 7.13 (s, 1H), 7.15 (d, 1H, *J* 7.8 Hz), 7.29 (d, 1H, *J* 7.8 Hz), 7.78 (s, 1H) and 8.5 (s, 1H); *m/z* 261 ($M^+$ + 1, 0.2%), 193 (58), 192 (45), 165 (36), 135 (100), 111 (45), 105 (38), 91 (37) and 84 (36) (Anal. Calc. for $C_{14}H_{16}ON_2S$: C, 64.59; H, 6.19; N, 10.76. Found: C, 64.66; H, 6.21; N, 10.69).

*D-(-)-Pantoyllactone 1-thiocarbonylimidazolide* **3i**. — Yield, 94%; m.p. 119~120 °C; $\nu_{max}/cm^{-1}$ 2973, 1793, 1465, 1397, 1324, 1288, 1224, 1123 and 1030;δ 1.26 (s, 3H), 1.33 (s, 3H), 4.17 (s, 2H), 6.27 (s, 1H), 7.08 (s, 1H), 7.65 (s, 1H) and 8.38 (s, 1H); *m/z* 241 ($M^+$ + 1, 32), 240 ($M^+$, 23%), 172 (60), 112 (61), 69 (58), 68 (55), 43 (93) and 41 (100); Anal. Calc. for $C_{10}H_{12}O_3N_2S$: C, 49.99; H, 5.03; N, 11.66. Found: C, 49.8; H, 5.11; N, 11.71.

*Methyl (1S,2R,4aR,8S,8aR)-8-(imidazol-1-ylthiocarbonyl)oxy-2-methyl-4-oxadeca-hydronaphthalene-1-carboxylate* **3j**. — Yield, 81%; m.p. 108~109 °C; $\nu_{max}/cm^{-1}$ 1726, 1713, 1388, 1333, 1284, 1236 and 991;δ 1.09 (d, 3H, *J* 7.3 Hz), 1.15 – 1.5 (m, 3H), 1.94 (m, 1H), 2.07 (dd, 1H, *J* 13, 2.2 Hz), 2.18 (dd, 1H, *J* 14, 2 Hz), 2.25~2.45 (m, 2H), 2.61 (m, 1H), 2.79 (d, 1H, *J* 2.8 Hz), 2.95 – 3.1 (m, 2H), 3.65 (s, 3H), 5.55 (td, 1H, *J* 10.5, 4.6 Hz), 7.07 (s, 1H), 7.62 (s, 1H) and 8.33 (s, 1H); *m/z* 319 ($M^+$ – MeO, 3%), 223 (89), 222 (64), 163 (100), 121 (45) and 69 (50) (Anal. Calc. for $C_{17}H_{22}O_4N_2S$: C, 58.27; H, 6.33; N, 7.99. Found: C, 58.5; H, 6.3; N 8.0).

*2-Adamanthyl 1-thiocarbonylimidazolide* **3k**. — Yield, 18% [2-adamantanol (80%) was recovered]; m.p. 74~75 °C; $\nu_{max}/cm^{-1}$ 2932, 1465, 1452, 1387, 1380, 1360, 1327, 1284, 1246, 1100 and 983;δ 1.7 – 2.1 (m, 12H), 2.31 (s, 2H), 5.64 (s, 1H), 7.05 (s, 1H), 7.68 (s, 1H) and 8.39 (s, 1H); *m/z* 262 ($M^+$, 11%), 202 (35), 175 (36), 135 (100), 93 (40), 79 (38) and 67 (47) (Anal. Calc. for $C_{14}H_{18}ON_2S$: C, 64.09; H, 6.92; N, 10.68. Found: C, 63.87; H, 6.88; N, 11).

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(*Received in Japan* 11 *November* 1996; *accepted* 19 *December* 1996)