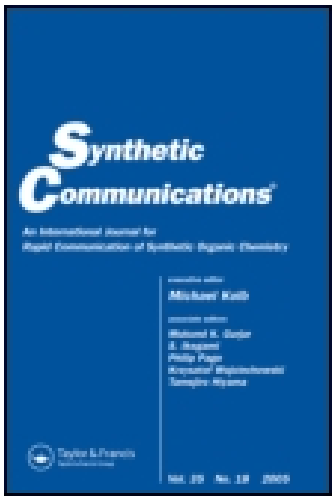

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

SYNTHESIS OF IMIDAZOYLTHIOCARBONYL INTERMEDIATES FOR THE RADICAL DEOXYGENATION OF HINDERED SECONDARY ALCOHOLS

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Published online: 09 Nov 2006.

To cite this article: Daniel Oves , Mónica Díaz , Susana Fernández , Miguel Ferrero & Vicente Gotor (2001) SYNTHESIS OF IMIDAZOYLTHIOCARBONYL INTERMEDIATES FOR THE RADICAL DEOXYGENATION OF HINDERED SECONDARY ALCOHOLS, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:15, 2335-2343, DOI: 10.1081/SCC-100104834

To link to this article: http://dx.doi.org/10.1081/SCC-100104834

SYNTHETIC COMMUNICATIONS, 31(15), 2335–2343 (2001)

SYNTHESIS OF IMIDAZOYLTHIOCARBONYL INTERMEDIATES FOR THE RADICAL DEOXYGENATION OF HINDERED SECONDARY ALCOHOLS

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ABSTRACT

A practical and efficient synthesis of imidazoylthiocarbonyl derivatives of highly hindered alcohols was achieved using 1,1′-thiocarbonyldiimidazole in very concentrated mixtures of reagents. More diluted conditions give longer reaction times and the recovery of unreacted starting alcohol.

Radical deoxygenation of alcohols is an important process in organic synthesis.[1] Barton and McCombie[2] have shown that secondary alcohols can be deoxygenated by a radical chain reduction of suitable thiocarbonyl derivatives using tributyltin hydride and 2,2′-azobis(2-methylpropionitrile) (AIBN) as initiator. Under typical deoxygenation conditions *S*-methyldithiocarbonyl,[3] thiobenzoyl,[4] imidazole-1-thiocarbonyl,[5] phenoxythiocarbonyl[6] or *S*-phenyldithiocarbonyl[7] derivatives, among others, afford the deoxy

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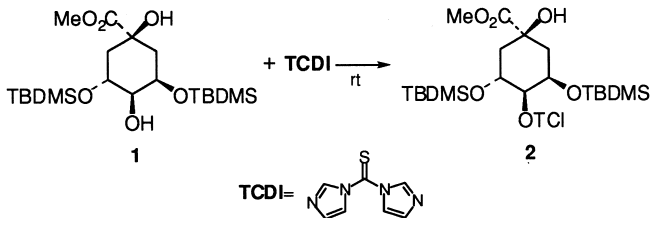
compound in high yield. The choice of the thiocarbonyl compound is determined more by structural features present in the alcohol than by the actual reductive step.

Quinic acid, shikimic acid, and their derivatives are useful precursors in the synthesis of important natural compounds. The chiral centres present in their structures and the possible introduction of a variety of new functions from the selective manipulation of the functional groups on the cyclohexane ring makes these starting materials very attractive from the point of view of organic synthesis.

In our ongoing research into the synthesis of A-ring precursors of vitamin D_3 analogues[8] it was necessary to obtain the corresponding thioimidazolide derivative of various intermediates.[9] Conventional procedures reported in the literature[5,10] involve the reaction of an alcohol with an excess of 1,1′-thiocarbonyldiimidazole (TCDI) in methylene chloride, 1,2-dichloroethane or tetrahydrofuran at room temperature or under reflux. However, low isolated yields of thioimidazolide compounds were obtained when these conditions were employed in sterically hindered substrates, in which the reactive hydroxyl function is surrounded by two *O*-*tert*-butyldimethylsilyl groups. This bulky protecting group is very commonly used to regioselectively protect one hydroxyl group among others and to ensure the stability of the silyl ether, which is linked to the steric bulk of the substituents on the silicon atom, for the successive transformations on the molecule.

In view of our unsuccessful experiments, we were encouraged to investigate the appropriate conditions to perform the synthesis of thioimidazolides efficiently.

DeLuca and co-workers have reported[10a] the synthesis of compound **2** with 91% yield by reaction of 3,5-disilylprotected quinate **1** with 1.6 equivalents of TCDI in methylene chloride at room temperature in 60 h (Scheme 1).



Scheme 1.

When the same conditions were applied by us, GC analysis showed thiomidazolide **2** as the minor compound after 96 h at room temperature,

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Table 1. Reaction Conditions to Prepare Thioimidazolide Derivative **2** from **1**

Entry	**1** (mmol)	TCDI[a] (equiv.)	CH_2Cl_2 (ml)	t (h)	conv (%) [**2**, yield[b] (%)]
1	0.23	1.6 (A)	1.3	96	16[c]
2	0.23	2.0 (C)	1.3	120	> 98[c] [55]
3	4.60	1.6 + 1[d] (C)	20.0	120	> 99[c] [83]
4	0.23	1.2 (A)	drops[e]	48	52[c]
5	0.23	1.2 (B)	drops[e]	32	78[c]
6	0.23	1.2 (C)	drops[e]	24	83[f]
7	0.23	1.2 (D)	drops[e]	24	100[f] [76]
8	5.70	1.2 (C)	6.0	8	100[f] [89]

[a]Different batches: A and B were approximately five months old, C had been open approx, three weeks, and D opened just before starting the reactions. [b]The numbers in square brackets represents isolated yields of **2** for processes that are close to 100% conversion. [c]Calculated by GC. [d]After 3 days, an extra equivalent was added. [e]Minimum amount of solvent required to dissolve the reagents. [f]Calculated by NMR.

together with large amounts of starting material (entry 1, Table 1). With the aim of increasing the degree of conversion, a larger excess of TCDI (2 equiv.) was used (entry 2, Table 1). Thus, after five days, 98% of conversion was achieved, although unfortunately a mixture of 4-TCI derivative **2** and the corresponding 1,4-dithiocarbonyl compound, were obtained in a ratio 4.5:1. To avoid the formation of the latter, we added 1.6 equiv. at the beginning of the process, and an additional equiv. of TCDI after 3 days (the point at which the reaction did not evolve further), stirring being maintained for another two days (entry 3, Table 1). In these conditions, compound **2** was isolated with 83% yield after purification by flash chromatography column, and only traces of the 1,4-dithiocarbonyl derivative were obtained. The limitations, nevertheless, were the large excess of TCDI and the long reaction time needed.

After carrying out several experiments, we realized that both TCDI batch and concentration could play a role in this process. We decided to perform the experiments using different batches (mp and ^{1}H-NMR spectra of all of them are identical; see footnote *a* in Table 1) of TCDI, and the minimum amount of solvent needed to dissolve the reagents. Moreover, we carried out the reactions with only a slight excess of TCDI (1.2 equiv.) in order not to waste this reagent. The importance of the concentration in the course of the reaction was observed from entries 1 and 4 in Table 1. Even with the smaller amount of TCDI, a 52% conversion was obtained in only two days when just a few drops were used to dissolve the reagents, whilst in more

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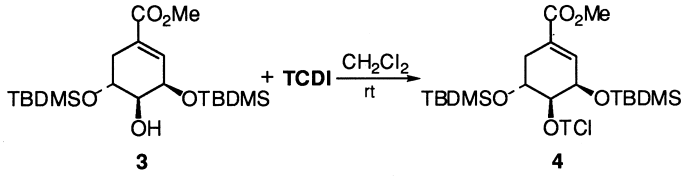
dilute conditions four days were necessary to obtain a 16% of conversion. If different batches of TCDI were used, shorter reaction times were needed to achieve compound **2** with the newer reagent (entries 4–7, Table 1). Thus, old batches of TCDI which were usually rejected because reactions did not evolve more than 15% in standard conditions, in concentrated conditions, now gave the desired product although in longer reaction times.

In order to scale-up the process, the reaction was carried out with 5.70 mmol of starting material and 1.2 equiv. of TCDI in 6 ml of methylene chloride (entry 8, Table 1). Thus, derivative **2** was obtained in 8 h with 89% isolated yield after purification by silica gel column.

Similar results were obtained when the above conditions were applied to synthon **3** (Scheme 2).



3 **4**

Scheme 2.

Thus, entries 1 *vs.* 2 and 3 *vs.* 4 in Table 2 show the concentration dependence in the formation of the corresponding imidazoylthiocarbonyl **4**. In highly concentrated conditions (entries 2 and 4, Table 2) total conversions were obtained in short periods of time (11 and 6 h respectively) in contrast to entries 1 and 3. The isolated yields were excellent (90–98%).

Table 2. Reaction Conditions to Prepare Thioimidazolide Derivative **4** from **3**

Entry	**3** (mmol)	TCDI[a] (equiv.)	CH_2Cl_2 (ml)	t (h)	conv[b] (%) [**4**, yield[c] (%)]
1	0.24	1.2 (C)	1.3	80	80
2	0.24	1.2 (C)	drops[d]	11	> 98 [90]
3	0.24	1.2 (D)	1.3	52	90
4	0.24	1.2 (D)	drops[d]	6	100 [98]

[a]Different batches: C had been open approx. three weeks, and D opened just before starting the reactions. [b]Conversion percentage of **3** calculated by NMR. [c]The numbers in square brackets represents isolated yields of **4** for processes close to 100% conversion. [d]Minimum amount of solvent required to dissolve the reagents.

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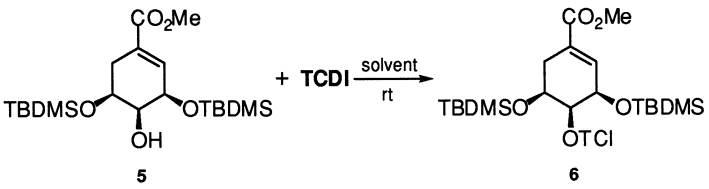
These concentrated conditions were essential in the case of the strongly sterically hindered substrate **5** (Scheme 3), which shows an inversion in the 5'-OTBDMS group with respect to compound **3**. This characteristic means that the substituents in positions 3, 4, and 5 are very close together in space, and consequently the steric effects are increased substantially. Thus, the reaction of **5** with TCDI in presence of *N*,*N*-dimethylaminopyridine as catalyst and methylene chloride as solvent takes place with less than 10% conversion after several days at room temperature followed by solvent reflux (entry 1, Table 3). The change from methylene chloride to THF did not improve the amount of **6** obtained.



Scheme 3.

On the other hand, when the smallest amount of solvent necessary to dissolve the reagents and substrate **5** was used (entry 3, Table 3), the thioimidazolide derivative **6** was obtained 86% yield in just 6 h at room temperature.

Table 3. Reaction Conditions to Prepare Thioimidazolide Derivative **6** from **5**

Entry	**5** (mmol)	TCDI[a] (equiv.)	Solvent (ml)	t (h)	conv[b] (%) [**6**, yield[c] (%)]
1	0.10	2.0	CH_2Cl_2 (3.0)	96[d]	< 10
2	0.12	2.5	THF (5.0)	96[d]	< 5
3	1.00	2.0	CH_2Cl_2 (1.0)	6	100 [86]

[a]Batch D (opened just before starting the reactions) was used with 0.5 equiv. DMAP as catalyst. [b]Conversion percentage of **5** calculated by GC. [c]The numbers in square brackets represent isolated yields of **6** for processes close to 100% conversion. [d]The reaction was carried out at rt for 3 d and 1 d under reflux.

In this paper, the concentration dependence of the preparation of thiomidazolide derivatives from highly sterically hindered alcohols has been demonstrated. The use of very concentrated solutions allows mild reaction conditions and short reaction times, in addition to saving reagents

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and solvent, and thus making the reaction more environmentally friendly. Moreover, old batches of TCDI can be used with these reaction conditions. This is an improvement for the radical deoxygenation through thiomidazolide intermediates of highly hindered alcohols that possess sensitive functional groups, to the conditions used to introduce more reactive thiocarbonyl compounds. These alcohols are present not only in derivatives described in this paper, but in structures *en route* to other complex molecules which possess very congested hydroxyl groups.

EXPERIMENTAL

General

Melting points were taken on samples in open capillary tubes using a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Mattson 3000 Infrared Fourier Transform spectrophotometer using NaCl plates. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh). ^{1}H-, ^{13}C-NMR, and DEPT were obtained using a Bruker AC-200 (^{1}H, 200.13 MHz and ^{13}C, 50.3 MHz) spectrometer for routine experiments. Bruker AMX-400 spectrometer operating at 400.13 and 100.61 MHz for ^{1}H and ^{13}C, respectively was used for the acquisition of ^{1}H-^{1}H homonuclear and ^{1}H-^{13}C heteronuclear correlation experiments. The chemical shifts are given in delta (δ) values and the coupling constants (J) in Hertz (Hz). Mass spectra (HRMS or MS) were recorded on a Finnigan MAT 95 spectrometer set at 70 eV EI (electron impact). The solvents were dried by standard methods described in the literature. Gas chromatography was carried out with flame ionization detection (FID) and a 25 m HP-1 capillary column coated with methylsilicone gum using nitrogen as carrier gas. The method used was: injector and detector temperatures set at 300°C, column initial temperature 250°C (3 min), rate 18°C/min, column final temperature 280°C (10 min). With this method, compound **1** appeared at 4.8 min; **2** at 12.0 min; **5** at 5.7 min; and **6** at 12.6 min. Hydroxyquinate **1** was synthesised as has been reported previously.[10a] Shikimate **3** was first reported by Desmaele and Tanier.[11] 3,5-Disilyl protected compound **5** was obtained from selective bis-protection of (−)-methyl 5-*epi*-shikimate.[8c]

General Procedure

1,1′-Thiocarbonyldiimidazole was added to a solution of the alcohol in methylene chloride or THF under nitrogen atmosphere (see details in Tables

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1, 2, and 3). The reaction mixture was stirred and monitored by GC. When the reaction did not evolve further, the solvent was evaporated under reduced pressure and the crude was purified by flash chromatography using as eluent 40% EtOAc/hexane for compound **2**, 15% EtOAc/hexane for **4**, and 10% EtOAc/hexane for **6**. Yields are indicated in the tables.

Methyl (1s_n,3*R*,4s_n,5*R*)-3,5-di[(*tert*-Butyldimethylsilyl)oxy]-1-hydroxy-4-[(imidazoylthioncarbonyl)oxy]cyclohexanecarboxylate (2). This compound was previously reported.[10a] **IR** (NaCl): *v* 3250, 2953, 2923, 2887, 2857, 1742, and 1532 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ −0.12 (s, 3H, *Me*Si), 0.00 (s, 3H, *Me*Si), 0.06 (s, 3H, *Me*Si), 0.08 (s, 3H, *Me*Si), 0.76 (s, 9H, Me_3Csi), 0.89 (s, 9H, Me_3CSi), 1.99 (dd, 1H, $^2J_{HH}$ 13.3, $^3J_{HH}$ 10.1 Hz, H-6a), 2.07 (ddd, 1H, $^2J_{HH}$ 14.5, $^3J_{HH}$ 4.3, $^4J_{HH}$ 2.7 Hz, H-2e), 2.27 (dd, 1H, $^2J_{HH}$ 14.6, $^3J_{HH}$ 2.7 Hz, H-2a), 3.31 (ddd, 1H, $^2J_{HH}$ 13.5, $^3J_{HH}$ 5.0, $^4J_{HH}$ 2.7 Hz, H-6e), 3.79 (s, 3H, O*Me*), 4.56 (ddd, 1H, $^3J_{HH}$ 10.1, 9.0, 4.9 Hz, H-5), 4.64 (ddd, 1H, $^3J_{HH}$ 4.4, 2.8, 2.8 Hz, H-3), 5.50 (dd, 1H, $^3J_{HH}$ 9.0, 2.7 Hz, H-4), 7.05 (m, 1H, H-im), 7.62 (m, 1H, H-im), and 8.37 (m, 1H, H-im); **^{13}C NMR** ($CDCl_3$, 50.3 MHz): δ −6.0 (*Me*Si), −5.3 (*Me*Si), −5.1 (*Me*Si), −4.5 (*Me*Si), 17.3 (Me_3*C*Si), 17.4 (Me_3*C*Si), 25.1 (Me_3CSi), 25.3 (Me_3CSi), 37.6, 42.6 (C-2 and C-6), 52.4 (O*Me*), 65.1, 68.0 (C-3 and C-5), 74.8 (C-1), 87.5 (C-4), 117.4 (im), 130.5 (im), 136.8 (im), 173.1 (C=O), and 183.5 (C=S); **MS** (70 eV, *m*/*z*): 487 (M^+-^{t}Bu, 10%), 427 (9), 359 (21), 267 (47), 227 (40), 185 (54), and 73 (100); **HRMS**: Calcd for $C_{20}H_{35}N_2O_6SSi_2$: 487.1754. Found: 487.1754.

Methyl (3*R*,4*S*,5*R*)-3,5-di[(*tert*-Butyldimethylsilyl)oxy]-4-[(imidazoyl-thiocarbonyl)oxy]cyclohex-1-enecarboxylate (4). **IR** (NaCl): *v* 3135, 2940, 1722, 1656, 1531, and 1470 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ −0.01 (s, 3H, *Me*Si), 0.08 (s, 3H, *Me*Si), 0.10 (s, 6H, *Me*Si), 0.81 (s, 9H, Me_3CSi), 0.83 (s, 9H, Me_3CSi), 2.29–2.68 (m, 2H, H-6), 3.76 (s, 3H, O*Me*), 4.44 (m, 1H, H-5), 4.30 (br s, 1H, H-3), 5.62 (m, 1H, H-4), 6.77 (m, 1H, H-2), 6.99 (br s, 1H, H-im), 7.54 (br s, 1H, H-im), and 8.36 (br s, 1H, H-im); **^{13}C-NMR** ($CDCl_3$, 50.3 MHz): δ −5.2 (*Me*Si), −5.0 (*Me*Si), −4.94 (*Me*Si), −4.89 (*Me*Si), 17.6 (Me_3*C*Si), 17.7 (Me_3*C*Si), 25.40 (Me_3CSi), 25.43 (Me_3CSi), 31.1 (C-6), 51.9 (O*Me*), 64.8, 65.0 (C-3 and C-5), 81.3 (C-4), 117.8 (im), 128.3 (C-1), 130.7 (im), 136.7 (im), 137.4 (C-2), 166.4 (C=O), and 183.9 (C=S); **MS** (70 eV, *m*/*z*): 526 (M^+, 5%), 469 (100), 409 (41), 341 (51), 267 (42), 235 (31), and 185 (68); **HRMS**: Calcd for $C_{24}H_{42}N_2O_5SSi_2$: 526.2353. Found: 526.2342.

Methyl (3*R*,4*S*,5*S*)-3,5-di[(*tert*-Butyldimethylsilyl)oxy]-4-[(imidazoyl-thiocarbonyl)oxy]cyclohex-1-enecarboxylate (6). **IR** (NaCl): *v* 3134, 2949, 2897, 1722, 1656, 1531, and 1464 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz): δ 0.07 (s, 3H, *Me*Si), 0.09 (s, 3H, *Me*Si), 0.10 (s, 3H, *Me*Si), 0.11 (s, 3H, *Me*Si), 0.77 (s, 9H, Me_3CSi), 0.84 (s, 9H, Me_3CSi), 2.39 (m, 1H, H-6),

2.70 (dd, 1H, $^{2}J_{HH}$ 17.5, $^{3}J_{HH}$ 6.4 Hz, H-6), 3.80 (s, 3H, O*Me*), 4.09 (m, 1H, H-5), 4.62 (m, 1H, H-3), 6.13 (m, 1H, H-4), 6.61 (m, 1H, H-2), 6.99 (s, 1H, H-im), 7.54 (s, 1H, H-im), and 8.22 (s, 1H, H-im); **^{13}C NMR** ($CDCl_3$, 50.3 MHz): δ −5.1 (*Me*Si), −5.05 (*Me*Si), −5.02 (*Me*Si), −4.9 (*Me*Si), 17.8 (Me_3*C*Si), 17.9 (Me_3*C*Si), 25.4 (*Me*$_3$CSi), 25.5 (*Me*$_3$CSi), 30.3 (C-6), 52.1 (O*Me*), 67.5 (C-5), 68.2 (C-3), 82.1 (C-4), 118.0 (im), 128.7 (C-1), 130.5 (im), 136.7 (im), 138.2 (C-2), 166.2 (C=O), and 184.8 (C=S); **MS** (70 eV, *m*/*z*): 526 (M^+, < 1%), 469 (35), 341 (21), 267 (79), 227 (46), 185 (90), and 73 (100); **HRMS**: Calcd for $C_{24}H_{42}N_2O_5SSi_2$: 526.2353. Found: 526.2351.

ACKNOWLEDGMENTS

Financial support from Comisión Interministerial de Ciencia y Tecnología (Spain; Project BIO98-0770) and Fundación Príncipe de Asturias (''Dr. Severo Ochoa'' Award to M.F.) is gratefully acknowledged. We also thank the Ministerio de Educación y Cultura (Spain) for post-doctoral fellowships (S.F. and M.F.).

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Received in the UK September 18, 2000

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