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Electrophilic α -Thiocyanation of Chiral and Achiral N-Acyl Imides. A Convenient Route to 5-Substituted and 5,5-Disubstituted 2,4-Thiazolidinediones

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Abstract

Electrophilic α -thiocyanation of N-acyl carboximides using N-thiocyanatosuccinimide and hydrolytic cyclization of the adducts affords 5-substituted and 5,5-disubstituted 2,4-thiazolidinediones in good overall yields. α -Thiocyanation of chiral N-acyl carboximides proceeds with excellent diastereoselectivity, although partial racemization occurs during subsequent cyclization.

Keywords

Thiocyanate; thiazolidinedione; enolate; asymmetric; heterocycle

The 2,4-thiazolidinedione (TZD) moiety is extensively utilized as a carboxylic acid mimetic to improve the metabolic stability and therapeutic profile of bioactive agents.¹ TZDs are often prepared from the parent carboxylates via a three-step sequence of α -halogenation, nucleophilic displacement with thiourea² or KSCN,³ and hydrolytic ring closure, although this route can be problematic for 5,5-disubstituted thiazolidinediones⁴ and/or if sensitive functionality is present.⁵ Consequently, we sought an alternative procedure and report herein the direct α -thiocyanation of N-acyl carboximides **1** (R = H) using N-thiocyanatosuccinimide⁶ (**2**) and hydrolytic cyclization of the adducts **3** to TZDs **4** in good overall yields (eq 1). Notably, α -thiocyanation of chiral **1** (R = PhCH₂–) proceeded with excellent diastereoselectivity, although partial racemization occurred during cyclization to **4**.

Based upon earlier studies by Toste *et al.*,⁶ we selected N-thiocyanatosuccinimide (**2**) as a convenient source of S-electrophilic thiocyanate. However, extensive efforts to add **2** to enolic intermediates generated from carboxylic acids and esters routinely afforded little if any of the desired α -thiocyanate adduct. N-acyl carboximides **1** (R = H), in sharp contrast, reacted smoothly with **2** following the Evans' protocol⁷ (Method A⁸) to give **3** in good yields (Table 1).⁹ The reaction was compatible with an electron rich aryl (Entry 1), sulfur heterocycle (Entry

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2), terminal and disubstituted acetylenes (Entries 3 and 4), terminal olefin (Entry 5), and vinyl dibromide (Entry 6). α -Phenoxy carboximide **23** (Entry 7), on the other hand, proved recalcitrant as the boron enolate, but could be coaxed to react with **2** by way of its lithium salt (Method B⁸).

Cyclization to the corresponding TZDs **4** (Table 1) was best done with a two-step, one-pot process via initial methoxide addition to the thiocyanate with concomitant annulation and then acidic hydrolysis of the resultant 2-methoxythiazol-4(5*H*)-ones.¹⁰ Not surprisingly, **25** was hydrolytically labile and could not be isolated in any significant amount. Analogous α -thiocyanations of 4(*R*)-phenylmethyl-2-oxazolidinones⁷ **26** (Entry 1) and **28** (Entry 2) via Method A proceeded in good yields and with virtually complete diastereoselectivities (Table 2). By analogy with comparable boron enolate azidations and brominations, adducts **27** and **29** were assigned the 2*R*-stereochemistry. α,α -Disubstituted carboxamides **30a**¹¹ and **b** (Entry 3) reacted sluggishly under the same conditions, so we adapted Kobayashi's protocol¹² [LDA, Ti(O-*i*Pr)₃Cl] for the α -thiocyanation (Method C8). The same chromatographically separable 1:1 mixture of diastereomers **31a** and **b** was obtained starting from either **30a** or **b**. All efforts to convert thiocyanates **27** and **29** to TZDs using the above and related hydrolytic conditions induced complete racemization at the C(2)-stereogenic centers. Reasoning that the α -hydrogen would be less prone to epimerization if the thiocyanate was transformed into a thiocarbamate, we developed an exceptionally mild procedure utilizing the Ghaffar-Parkins' catalyst in THF/water.¹³ In practice, **32** was obtained from **27** in excellent yield and with no indication of epimerization by ¹H/¹³C NMR analysis (Scheme 1). Unfortunately, cyclization to **33**, even at low temperature, resulted in some loss of C(2)-stereochemical integrity as determined by chiral HPLC.^{14,15}

As anticipated, cyclizations of thiocyanates **31a** and **b**, which lack epimerizable α -hydrogens, using either of the above annulation procedures were uneventful and the derived 5,5-disubstituted TZDs **34a** and **b** were secured as single enantiomers¹⁴ in ca. 70% yield.

Supplementary data

Supplementary data Supplementary data associated with this article can be found in the online version, at doi:

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References and notes

- (a) Boyd AS. *Int. J. Derm* 2007;46:557. [PubMed: 17550551] (b) McIntyre RS, Soczynska JK, Woldeyohannes HO, Lewis GF, Leiter LA, MacQueen GM, Miranda A, Fulgosi D, Konarski JZ, Kennedy SH. *Expert Opin. Pharmacother* 2007;8:1615. [PubMed: 17685880] (c) Elte JWF, Blickle JF. *Eur. J. Inter. Med* 2007;18:18.

2. Momose Y, Maekawa T, Yamano T, Kawada M, Odaka H, Ikeda H, Sohda T. *J. Med. Chem.* 2002;45:1518. [PubMed: 11906293]
3. Sohda T, Mizuno K, Kawamatsu Y. *Chem. Pharm. Bull.* 1984;32:4460. [PubMed: 6532548]
4. Doran WJ, Shonle HA. *J. Org. Chem.* 1938;3:193.
5. Alternative syntheses: (a) Metwally M, Etman H, Keshk E, Fekry A. *Phosphorus, Sulfur Silicon Relat. Elem* 2006;181:1039. (b) Hu B, Malamas M, Ellingboe J, Largis E, Han S, Mulvey R, Tillett J. *Bioorg. Med. Chem. Lett* 2001;11:981. [PubMed: 11327605] (c) Singh SP, Parmar SS, Raman K, Stenberg VI. *Chem. Rev* 1981;81:175. (d) Gaupp S, Effenberger F. *Tetrahedron: Asymm* 1999;10:1777.
6. Toste FD, De Stefano V, Still IW. *J. Synth. Commun* 1995;25:1277.
7. Evans DA, Britton TC, Ellman JA, Dorow RL. *J. Am. Chem. Soc* 1990;112:4011.
8. **Method A:** *n*-Bu₂BOTf (1 M soln in CH₂Cl₂, 1.1 mmol) was added with stirring to a 0°C solution of N-acyl imide **1** (1 mmol) in CH₂Cl₂ (10 mL) under an argon atmosphere followed by neat (*i*-Pr)₂NEt (1.2 mmol). After 1 h, the resultant slurry was cooled to -78°C and a solution of **2** (2 mmol) in CH₂Cl₂ (12 mL) was slowly added via syringe. After 1.5 h, the reaction was quenched using pH 7 phosphate buffer (3.5 mL) and 30% H₂O₂ (22 mmol). Hydrogen peroxide was omitted during the quenching of adducts **9**, **21**, and **29**. Extractive isolation and purification by SiO₂ chromatography gave α-thiocyanate **3** in the indicated yields (Table 1). **Method B:** A precooled (-78°C) solution of N-acyl imide **1** (1 mmol) in dry THF (10 mL) was added via cannula to a stirring, -78°C solution of LDA (1.2 mmol) in dry THF (6 mL) under an argon atmosphere. After stirring for 30 min, a freshly prepared solution of **2** (2 mmol) in dry THF (3 mL) was added dropwise and the reaction mixture was allowed to stir for 2 h at -78°C. The reaction mixture was quenched with saturated aq. NH₄Cl (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄), concentrated in vacuo, and the residue was purified by SiO₂ column chromatography to give α-thiocyanate **3** in the indicated yield (Table 1). **Method C:** A precooled (-78°C) solution of N-acyl imide **30a** or **b** (1 mmol) in dry THF (15 mL) was added via cannula to a stirring, -78°C solution of LDA (2 mmol) in dry THF (12 mL) under an argon atmosphere. After 30 min, Ti(*O*-*i*Pr)₃Cl (4 mmol, 1 M soln in hexane) was added and the reaction mixture was warmed to -40°C. After 1 h, the mixture was re-cooled to -78°C and a freshly prepared solution of **2** (2 mmol) in dry THF (3 mL) was added dropwise. After 2 h at -78°C, the reaction mixture was quenched with saturated aq. NH₄Cl (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄), concentrated in vacuo, and the residue was purified by PTLC to give **31a** and **b** (66% combined yield, 1:1). PTLC: benzene/ether (96:4), **31a** and **b** R_f ~ 0.67 and 0.61, respectively. The absolute configurations of **31a** and **b** are based upon comparisons of ¹H/¹³C NMR and are tentative.
9. Spectral and physical data for representative compounds: **5**: pale yellow solid, mp 78.8-80.6°C; TLC: EtOAc/hexane (3:7), R_f ~ 0.39; ¹H NMR (CDCl₃, 300 MHz) δ 7.11 (d, 2 H, *J* = 8.4 Hz), 6.82 (d, 2 H, *J* = 8.4 Hz), 4.32 (t, 2 H, *J* = 8.1 Hz), 3.98 (t, 2 H, *J* = 8.1 Hz), 3.78 (s, 3 H), 2.94 (t, 2 H, *J* = 7.8 Hz), 2.63 (t, 2 H, *J* = 7.8 Hz), 1.96 (apparent p, 2 H, *J* = 7.5 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 173.5, 158.0, 153.7, 133.8, 129.6, 113.9, 62.25, 55.4, 42.7, 34.7, 34.4, 26.3. **6**: TLC: EtOAc/hexane (3:7), R_f ~ 0.37; ¹H NMR (CDCl₃, 300 MHz) δ 7.09 (d, 2 H, *J* = 6.3 Hz), 6.82 (d, 2 H, *J* = 6.3 Hz), 4.82 (t, 1 H, *J* = 9.3 Hz), 4.51-4.36 (m, 2 H), 4.23-3.92 (m, 2 H), 3.77 (s, 3 H), 2.85-2.65 (m, 2 H), 2.53-2.25 (m, 2 H); ¹³C NMR (CDCl₃, 100 MHz) δ 167.9, 158.2, 153.1, 131.1, 129.4, 113.9, 109.2, 62.4, 55.2, 45.1, 42.5, 32.6, 31.6. **7**: mp 74.2-76.6°C; TLC: EtOAc/hexane (3:7), R_f ~ 0.48; ¹H NMR (CDCl₃, 400 MHz) δ 8.02 (br s, 1 H, NH), 7.08 (d, 2 H, *J* = 8.8 Hz), 6.83 (d, 2 H, *J* = 8.8 Hz), 4.17 (dd, 1 H, *J* = 16, 4.4 Hz), 3.78 (s, 3 H), 2.83-2.65 (m, 2 H), 2.53-2.44 (m, 1 H), 2.23-2.13 (m, 1 H); ¹³C NMR (CDCl₃, 75 MHz) δ 174.7, 170.3, 158.6, 131.2, 129.8, 114.4, 55.5, 50.9, 35.0, 32.4. **8**: mp 76.7-77.7°C; TLC: EtOAc/hexane (2:3), R_f ~ 0.4; ¹H NMR (CDCl₃, 300 MHz) δ 7.10 (d, 1 H, *J* = 5.1 Hz), 6.91 (dd, 1 H, *J* = 5.1, 3.3 Hz), 6.81 (d, 1 H, *J* = 3.3 Hz), 4.39 (t, 2 H, *J* = 7.8 Hz), 4.00 (t, 2 H, *J* = 7.8 Hz), 2.99 (t, 2 H, *J* = 7.2 Hz), 2.91 (t, 2 H, *J* = 7.2 Hz), 2.05 (apparent p, 2 H, *J* = 7.2 Hz); ¹³C NMR (CDCl₃, 75 MHz) δ 173.1, 153.7, 144.4, 126.9, 124.7, 123.4, 62.2, 42.6, 34.5, 29.3, 26.3. **9**: TLC: EtOAc/hexane (3:7), R_f ~ 0.35; ¹H NMR (CDCl₃, 400 MHz) δ 7.13-7.05 (d, 1 H, *J* = 5.2 Hz), 6.91 (dd, 1 H, *J* = 5.1, 3.3 Hz), 6.82 (d, 1 H, *J* = 3.3 Hz), 4.84 (t, 1 H, *J* = 8 Hz), 4.49-4.40 (m, 2 H), 4.11-3.96 (m, 2 H), 3.06-3.02 (m, 2 H), 2.57-2.35 (m, 2 H); ¹³C NMR (CDCl₃, 100 MHz) δ 167.9, 153.4, 141.9, 127.3, 125.6, 124.3, 109.3, 62.8, 45.1, 42.8, 32.7, 26.7. **10**: mp 67.7-70.2°C; TLC: EtOAc/hexane (3:7, 3 elutions), R_f ~ 0.38; ¹H NMR (CDCl₃, 400 MHz) δ 8.95 (s, 1 H, NH), 7.17 (d, 1 H, *J* = 4.8 Hz), 6.93 (dd, 1 H, *J* = 4.8, 3.4 Hz), 6.83 (d, 1 H, *J* = 3.4 Hz), 4.25 (dd, 1 H, *J* = 9.6, 4.4 Hz), 3.22-2.86 (m, 2 H), 2.61-2.53 (m, 1 H), 2.30-2.17 (m, 1 H); ¹³C NMR (CDCl₃, 75 MHz)

δ 175.3, 171.0, 141.6, 127.3, 125.7, 124.4, 50.6, 35.0, 27.4. **26**: mp 70.8–71.6°C; TLC: EtOAc/hexane (2:3), $R_f \sim 0.44$; ^1H NMR (CDCl_3 , 300 MHz) δ 7.35–7.19 (m, 5 H), 7.13 (d, 2 H, $J = 9$ Hz), 6.83 (d, 2 H, $J = 9$ Hz), 4.69–4.59 (m, 1 H), 4.12–4.21 (m, 2 H), 3.78 (s, 3H), 3.28 (dd, 1 H, $J = 13.2$, 3.3 Hz), 3.08–2.88 (m, 2 H), 2.74 (dd, 1 H, $J = 13.2$, 3.3 Hz), 2.68–2.63 (m, 2 H), 2.04–1.93 (m, 2 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 172.9, 157.7, 153.3, 135.2, 133.4, 129.3, 128.8, 127.2, 113.6, 66.0, 55.1, 54.9, 37.7, 34.8, 34.1, 25.9; $[\alpha]_{23}^D -43.7$ (c 1.34, CHCl_3). **27**: mp 108.3–109.9°C; TLC: EtOAc/hexane (3:7), $R_f \sim 0.30$; ^1H NMR (CDCl_3 , 300 MHz) δ 7.35–7.20 (m, 5 H), 7.10 (d, 2 H, $J = 8.8$ Hz), 6.82 (d, 2 H, $J = 8.8$ Hz), 4.76 (t, 1 H, $J = 7.2$ Hz), 4.63–4.56 (m, 1 H), 4.24–4.16 (m, 2 H), 3.76 (s, 3 H), 3.29 (dd, 1 H, $J = 13.6$, 3.2 Hz), 2.86–2.79 (m, 2 H), 2.75–2.67 (m, 2 H), 2.55–2.45 (m, 1 H), 2.39–2.28 (m, 1 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 168.0, 158.6, 153.3, 134.7, 131.7, 129.8, 129.7, 129.3, 127.8, 114.3, 109.4, 69.9, 55.5, 55.4, 45.4, 37.6, 32.6, 31.9; $[\alpha]_{25}^D -110.1$ (c 1.05, CHCl_3). **28**: mp 46.8–48.2°C; TLC: EtOAc/hexane (2:3), $R_f \sim 0.40$; ^1H NMR (CDCl_3 , 400 MHz) δ 7.34–7.12 (m, 6 H), 6.92 (dd, 1 H, $J = 3.5$, 5.2 Hz), 6.83 (d, 1 H, $J = 3.5$ Hz), 4.68–4.63 (m, 1 H), 4.19–4.14 (m, 2 H), 3.27 (dd, 1 H, $J = 13.6$, 3.2 Hz), 3.04–2.92 (m, 4 H), 2.75 (dd, 1 H, $J = 13.2$, 9.6 Hz), 2.12–2.02 (m, 2 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.8, 153.5, 144.3, 135.4, 129.5, 129.1, 127.5, 126.9, 124.7, 123.4, 66.3, 55.2, 38.0, 34.8, 29.2, 26.2; $[\alpha]_{25}^D -48.1$ (c 1.01, CHCl_3). **29**: Pale yellow solid, mp 62.8–64.2°C; TLC: EtOAc/hexane (1:4, 2 elutions), $R_f \sim 0.30$; ^1H NMR (CDCl_3 , 300 MHz) δ 7.14–7.38 (m, 6 H), 6.92 (dd, 1 H, $J = 3.6$, 5.1 Hz), 6.84 (d, 1 H, $J = 3.6$ Hz), 4.79 (t, 1 H, $J = 9$ Hz), 4.71–4.61 (m, 1 H), 4.23 (d, 2 H, $J = 4.8$ Hz), 3.32 (dd, 1 H, $J = 13.5$, 2.7 Hz), 3.10–3.05 (m, 2 H), 2.90 (dd, 1 H, $J = 13.5$, 9.3 Hz), 2.70–2.38 (m, 2 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 167.7, 153.3, 141.9, 134.7, 129.7, 129.3, 127.8, 127.3, 125.6, 124.3, 109.2, 66.9, 55.5, 45.2, 37.6, 32.5, 26.7; $[\alpha]_{25}^D -79.25$ (c 0.81, CHCl_3).

10. **TZD Cyclization Procedure**: NaOMe (2.5 mmol) added with stirring to a 0°C solution of α -thiocyanate **3** (1 mmol) in dry MeOH/THF (4:1, 50 mL). After 1 h, the reaction mixture was acidified with 2 N HCl to pH 2. After stirring at rt for 3 h, the organic solvent was removed in vacuo and the aqueous residue was extracted with EtOAc (3 $\times$ 10 mL). The combined organic extracts were washed with water, dried, concentrated in vacuo and the residue purified by SiO_2 chromatography to give 2,4-thiazolidinedione **4** in the indicated yields (Table 1).
11. Imide **30** was prepared from racemic 2-methyl-3-phenylpropanoic acid and diastereomers **30a** and **b** were separated chromatographically [TLC: EtOAc/hexane (3:7), **30a,b** $R_f \sim 0.40$ and 0.38, respectively]. The absolute configuration of **30a** was established by saponification [$\text{LiOH}/\text{H}_2\text{O}_2$, THF/ H_2O (2:1), 0°C] and comparison of the free acid optical rotation with literature value: Lentz NL, Peet NP. *Tetrahedron Lett* 1990;31:811.
12. Murata Y, Kamino T, Hosokawa S, Kobayashi S. *Tetrahedron Lett* 2002;43:8121.
13. Ghaffar T, Parkins AW. *Tetrahedron Lett* 1995;36:8657.
14. Chiral HPLC of **33**: Chiralpak® AD (250 $\times$ 4.6 mm), hexane/*i*PrOH/AcOH (5:1:0.01), flow rate 1 mL/min, 230 nm, $R_t \sim 9.86$ and 14.61 min. For **34a,b**: $R_t \sim 6.4$ and 13.7 min, respectively.
15. The interconversion of 5-substituted TZD enantiomers under various conditions has been noted before: Welch CJ, Kress MH, Beconi M, Mathre DJ. *Chirality* 2003;15:143. [PubMed: 12520506] Shen Z, Bakhtiar R, Komuro M, Awano K, Taga F, Colletti A, Hora D, Feeney W, Iliff S, Franklin RB, Vincent S. *Rapid Commun. Mass Spec* 2005;19:1125. Also see references ² and ³

Scheme 1.

Reagents and conditions: (a) $\text{Pt}(\text{Me}_2\text{POH})_3$ (25 mol%), THF/ H_2O (2:1), 40°C, 2h; (b) LDA (1.2 equiv), THF/ Et_2O (2:1), -78°C, 2h.

Table 1

α -Thiocyanation of N-acyl imides and Hydrolytic Cyclization.

Entry	Carboximide	α -Thiocyanate	Yield (%)	TZD	Yield (%) ^a
1			78 ^b		78
2			74 ^b		66
3			69 ^b		62
4			71 ^b		68
5			72 ^b		71
6			71 ^b		68
7			54 ^c		0

^a (i) NaOMe, MeOH, 0°C; (ii) 2 N HCl, rt.

^b Prepared via Method A.

^c Prepared via Method B.

Table 2Asymmetric α -Thiocyanation of N-acyl imides.

Entry	Carboximide	α -Thiocyanate	Yield (%)	d.r. ^a
1	26	27	83 ^b	99:1
2	28	29	74 ^b	99:1
3	30a : R ¹ = H, R ² = Me 30b : R ¹ = Me, R ² = H	31a : R ¹ = Me, R ² = -SCN 31b : R ¹ = -SCN, R ² = Me	66 ^c	1:1

^a Determined by ¹H/¹³C NMR.^b Prepared via Method A.^c Prepared via Method C.

Stereochemical assignments are tentative.