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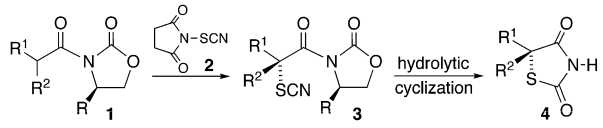
Abstract—Electrophilic α-thiocyanation of *N*-acyl carboximides using *N*-thiocyanatosuccinimide and hydrolytic cyclization of the adducts affords 5-substituted and 5,5-disubstituted 2,4-thiazolidinediones in good overall yields. α-Thiocyanation of chiral *N*-acyl carboximides proceeds with excellent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

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 thiourea[2] or KSCN,[3] and hydrolytic ring closure, although this route can be problematic for 5,5-disubstituted thiazolidinediones[4] 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*-thiocyanatosuccinimide[6] (**2**) and hydrolytic cyclization of adduct **3** to TZDs **4** in good overall yields (Eq. 1). Notably, α-thiocyanation of chiral **1** (R=$PhCH_2$—) proceeded with excellent diastereoselectivity, although partial racemization occurred during cyclization to **4**.



(1)

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[7] **1** (R=H), in sharp contrast, reacted smoothly with **2** following the Evans' protocol[7] (Method A[8]) to give **3** in good yields (Table 1).[9] The reaction was compatible with an electron rich aryl (Entry 1), sulfur heterocycle (Entry 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 B[8]).

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-oxazolidinones[7] **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 protocol[12] [LDA, Ti(*O*-*i*-Pr)$_3$Cl] for the α-thiocyanation (Method C8). The same chromatographically separable 1:1 mixture of diastereomers **31a** and **b** was obtained starting

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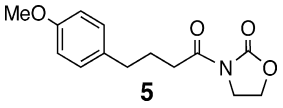
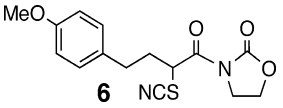
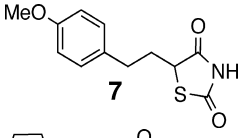
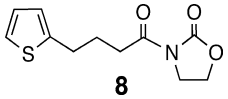
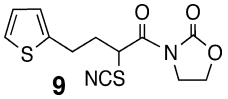
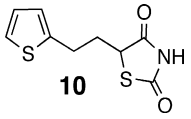
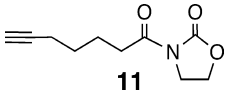
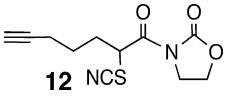
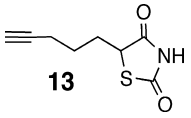
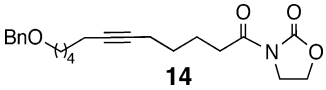
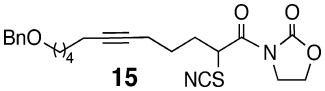
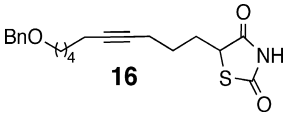
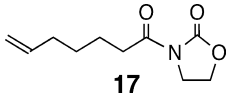
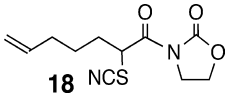
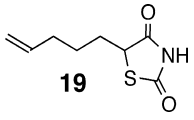
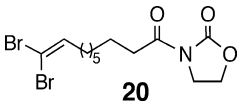
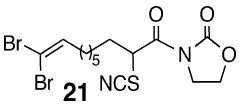
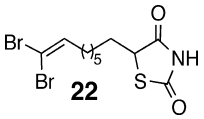
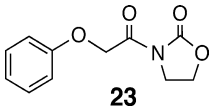
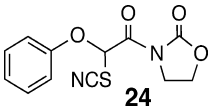
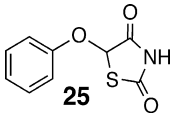
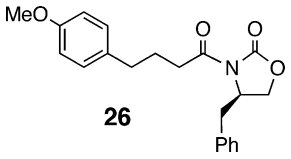
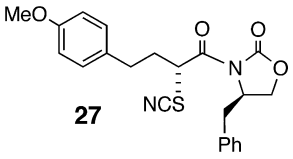
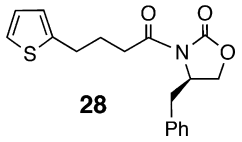
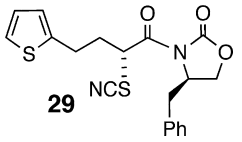
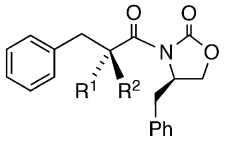
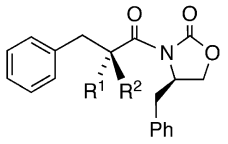
Table 1. α-Thiocyanation of *N*-acyl imides and hydrolytic cyclization

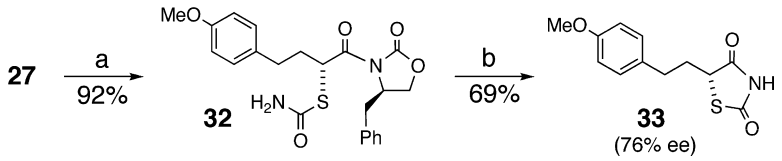
Entry	Carboximide	α-Thiocyanate	Yield (%)	TZD	Yield[a] (%)
1	 **5**	 **6**	78[b]	 **7**	78
2	 **8**	 **9**	74[b]	 **10**	66
3	 **11**	 **12**	69[b]	 **13**	62
4	 **14**	 **15**	71[b]	 **16**	68
5	 **17**	 **18**	72[b]	 **19**	71
6	 **20**	 **21**	71[b]	 **22**	68
7	 **23**	 **24**	54[c]	 **25**	0

[a] (i) NaOMe, MeOH, 0 °C; (ii) 2 N HCl, rt.
[b] Prepared via Method A.
[c] Prepared via Method B.

Table 2. Asymmetric 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

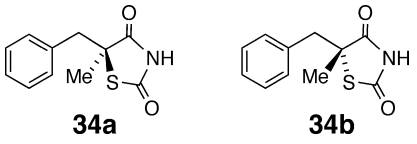
Stereochemical assignments are tentative.
[a] Determined by $^1H/^{13}C$ NMR.
[b] Prepared via Method A.
[c] Prepared via Method C.



Scheme 1. Reagents and conditions: (a) $Pt(Me_2POH)_3$ (25 mol%), THF/H_2O (2:1), 40 °C, 2 h; (b) LDA (1.2 equiv), THF/Et_2O (2:1), −78 °C, 2 h.

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 $^1H/^{13}C$ 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 enantiomers[14] in ca. 70% yield.



Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.02.034.

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7. Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.
8. *Method A*: *n*-Bu_2BOTf (1 M solution in CH_2Cl_2, 1.1 mmol) was added with stirring to a 0 °C solution of *N*-acyl imide **1** (1 mmol) in CH_2Cl_2 (10 mL) under an argon atmosphere followed by neat $(i\text{-Pr})_2NEt$ (1.2 mmol). After 1 h, the resultant slurry was cooled to −78 °C and a solution of **2** (2 mmol) in CH_2Cl_2 (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% H_2O_2 (22 mmol). Hydrogen peroxide was omitted during the quenching of adducts **9**, **21**, and **29**. Extractive isolation and purification by SiO_2 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 NH_4Cl (10 mL) and extracted with EtOAc (3× 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated in vacuo, and the residue was purified by SiO_2 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, $Ti(O\text{-}i\text{-}Pr)_3Cl$ (4 mmol, 1 M solution 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 NH_4Cl (10 mL) and extracted with EtOAc (3× 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), 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** $R_f \sim 0.67$ and 0.61, respectively. The absolute configurations of **31a** and **b** are based upon comparisons of $^1H/^{13}C$ NMR and are tentative.
9. Spectral and physical data for representative compounds: Compound **5**: pale yellow solid, mp 78.8–80.6 °C; TLC: EtOAc/hexane (3:7), $R_f \sim 0.39$; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.11 (d, 2H, $J = 8.4$ Hz), 6.82 (d, 2H, $J = 8.4$ Hz), 4.32 (t, 2H, $J = 8.1$ Hz), 3.98 (t, 2H, $J = 8.1$ Hz), 3.78 (s, 3H), 2.94 (t, 2H, $J = 7.8$ Hz), 2.63 (t, 2H, $J = 7.8$ Hz), 1.96 (apparent p, 2H, $J = 7.5$ Hz); ^{13}C

NMR ($CDCl_3$, 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.

Compound **6**: TLC: EtOAc/hexane (3:7), $R_f \sim 0.37$; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.09 (d, 2H, $J = 6.3$ Hz), 6.82 (d, 2H, $J = 6.3$ Hz), 4.82 (t, 1H, $J = 9.3$ Hz), 4.51–4.36 (m, 2H), 4.23–3.92 (m, 2H), 3.77 (s, 3H), 2.85–2.65 (m, 2H), 2.53–2.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 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.

Compound **7**: mp 74.2–76.6 °C; TLC: EtOAc/hexane (3:7), $R_f \sim 0.48$; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.02 (br s, 1H, NH), 7.08 (d, 2H, $J = 8.8$ Hz), 6.83 (d, 2H, $J = 8.8$ Hz), 4.17 (dd, 1H, $J = 16$, 4.4 Hz), 3.78 (s, 3H), 2.83–2.65 (m, 2H), 2.53–2.44 (m,1H), 2.23–2.13 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.7, 170.3, 158.6, 131.2, 129.8, 114.4, 55.5, 50.9, 35.0, 32.4.

Compound **8**: mp 76.7–77.7 °C; TLC: EtOAc/hexane (2:3), $R_f \sim 0.4$; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.10 (d, 1H, $J = 5.1$ Hz), 6.91 (dd, 1H, $J = 5.1$, 3.3 Hz), 6.81 (d, 1H, $J = 3.3$ Hz), 4.39 (t, 2H, $J = 7.8$ Hz), 4.00 (t, 2H, $J = 7.8$ Hz), 2.99 (t, 2H, $J = 7.2$ Hz), 2.91 (t, 2H, $J = 7.2$ Hz), 2.05 (apparent p, 2H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$, 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.

Compound **9**: TLC: EtOAc/hexane (3:7), $R_f \sim 0.35$; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.13–7.05 (d, 1H, $J = 5.2$ Hz), 6.91 (dd, 1H, $J = 5.1$, 3.3 Hz), 6.82 (d, 1H, $J = 3.3$ Hz), 4.84 (t, 1H, $J = 8$ Hz), 4.49–4.40 (m, 2H), 4.11–3.96 (m, 2H), 3.06–3.02 (m, 2H), 2.57–2.35 (m,2H); ^{13}C NMR ($CDCl_3$, 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.

Compound **10**: mp 67.7–70.2 °C; TLC: EtOAc/hexane (3:7, 3 elutions), $R_f \sim 0.38$; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.95 (s, 1H, NH), 7.17 (d, 1H, $J = 4.8$ Hz), 6.93 (dd, 1H, $J = 4.8$, 3.4 Hz), 6.83 (d, 1H, $J = 3.4$ Hz), 4.25 (dd, 1H, $J = 9.6$, 4.4 Hz), 3.22–2.86 (m, 2H), 2.61–2.53 (m, 1H), 2.30–2.17 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.3, 171.0, 141.6, 127.3, 125.7, 124.4, 50.6, 35.0, 27.4.

Compound **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, 5H), 7.13 (d, 2H, $J = 9$ Hz), 6.83 (d, 2H, $J = 9$ Hz), 4.69–4.59 (m, 1H), 4.12–4.21 (m, 2H), 3.78 (s, 3H), 3.28 (dd, 1H, $J = 13.2$, 3.3 Hz), 3.08–2.88 (m, 2H), 2.74 (dd, 1H, J =13.2, 3.3 Hz), 2.68–2.63 (m, 2H), 2.04–1.93 (m, 2H); ^{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, $CHCl_3$).

Compound **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, 5H), 7.10 (d, 2H, $J = 8.8$ Hz), 6.82 (d, 2H, $J = 8.8$ Hz), 4.76 (t, 1H, $J = 7.2$ Hz), 4.63–4.56 (m, 1H), 4.24–4.16 (m, 2H), 3.76 (s, 3H), 3.29 (dd, 1H, $J = 13.6$, 3.2 Hz), 2.86–2.79 (m, 2H), 2.75–2.67 (m, 2H), 2.55–2.45 (m, 1H), 2.39–2.28 (m, 1H); ^{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, $CHCl_3$).

Compound **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, 6H), 6.92 (dd, 1H, $J = 3.5$, 5.2 Hz), 6.83 (d, 1H, $J = 3.5$ Hz), 4.68–4.63 (m, 1H), 4.19–4.14 (m, 2H), 3.27 (dd, 1H, $J = 13.6$, 3.2 Hz), 3.04–2.92 (m, 4H), 2.75 (dd, 1H, $J = 13.2$, 9.6 Hz), 2.12–2.02 (m, 2H); ^{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, $CHCl_3$).

Compound **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, 6H), 6.92 (dd, 1H, $J = 3.6$, 5.1 Hz), 6.84 (d, 1H, $J = 3.6$ Hz), 4.79 (t, 1H, $J = 9$ Hz), 4.71–4.61 (m, 1H), 4.23 (d, 2H, $J = 4.8$ Hz), 3.32 (dd, 1H, $J = 13.5$, 2.7 Hz), 3.10–3.05 (m, 2H), 2.90 (dd, 1H, $J = 13.5$, 9.3 Hz), 2.70–2.38 (m, 2H); ^{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× 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** and **b** $R_f \sim 0.40$ and 0.38, respectively]. The absolute configuration of **30a** was established by saponification [$LiOH/H_2O_2$, THF/H_2O (2:1), 0 °C] and comparison of the free acid optical rotation with the literature value: Lentz, N. L.; Peet, N. P. *Tetrahedron Lett.* **1990**, *31*, 811.
12. Murata, Y.; Kamino, T.; Hosokawa, S.; Kobayashi, S. *Tetrahedron Lett.* **2002**, *43*, 8121.
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14. Chiral HPLC of **33**: Chiralpak® AD (250 × 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** and **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, C. J.; Kress, M. H.; Beconi, M.; Mathre, D. J. *Chirality* **2003**, *15*, 143; Shen, Z.; Bakhtiar, R.; Komuro, M.; Awano, K.; Taga, F.; Colletti, A.; Hora, D.; Feeney, W.; Iliff, S.; Franklin, R. B.; Vincent, S. *Rapid Commun. Mass Spectrom.* **2005**, *19*, 1125, also see Refs. 2 and 3.