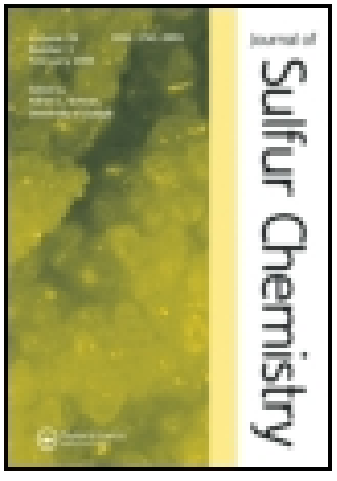

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A facile and effective synthesis of 4-imino-3-(arylidene)- azetidine-2-thiones via phosphorus pentasulfide

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A facile and effective synthesis of 4-imino-3-(arylidene)-azetidine-2-thiones via phosphorus pentasulfide

Ouafa Amiri[a], El Mostapha Rakib[a*], Medaghri-Alaoui Abdelouahid[a], Maria A.F. Faustino[b], Maria G.P.M.S. Neves[b] and José A.S. Cavaleiro[b]

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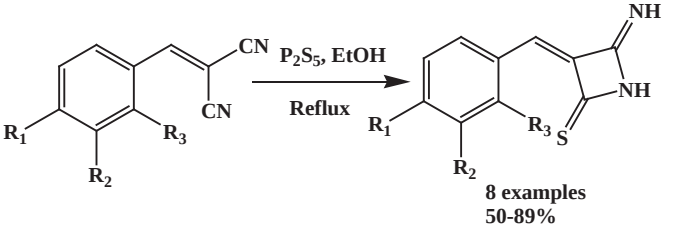
A new and an efficient synthesis of 4-imino-3-(arylidene)-azetidine-2-thiones is reported. The reaction of arylidenemalononitriles with phosphorus pentasulfide and ethanol affords the title products in good yields. Elemental analysis, infrared, ^{1}H NMR, ^{13}C NMR and mass spectral data elucidated structure of newly synthesized compounds.



Keywords: azetidine-2-thione; arylidenemalononitriles; phosphorus pentasulfide; ethanol

1. Introduction

2-Azetidinones, known as β-lactams, serve as synthons for much biologically important class of organic compounds. 2-Azetidinones and its derivatives display interesting biological activities such as antifungal, antimicrobial,[1–4] anti-inflammatory,[5–7] antitubercular,[8,9] antiplasmodial,[10] antidepressant,[11] antitumoral [12,13] and cholesterol absorption inhibitory properties.[14–16] 2-Azetidinones are not only useful in medicinal applications, but also used as intermediates and synthons for the production of several organic compounds.[17] Several synthetic methods have been developed for the preparation of the β-lactam ring.[18] Prompted by these observations and as part of our ongoing work on the development of azetidinones derivatives, herein we report a new method for the synthesis of 4-imino-3-(arylidene)-azetidine-2-thiones by reaction of arylidenemalononitriles with P_2S_5 in the presence of ethanol.

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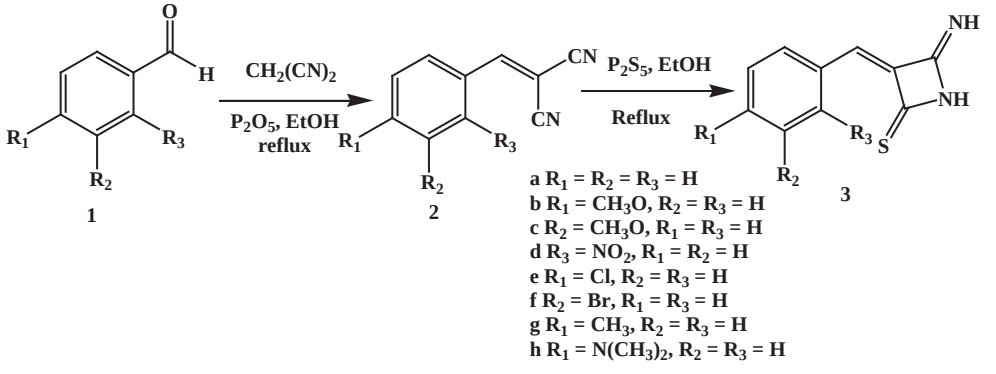
2. Results and discussion

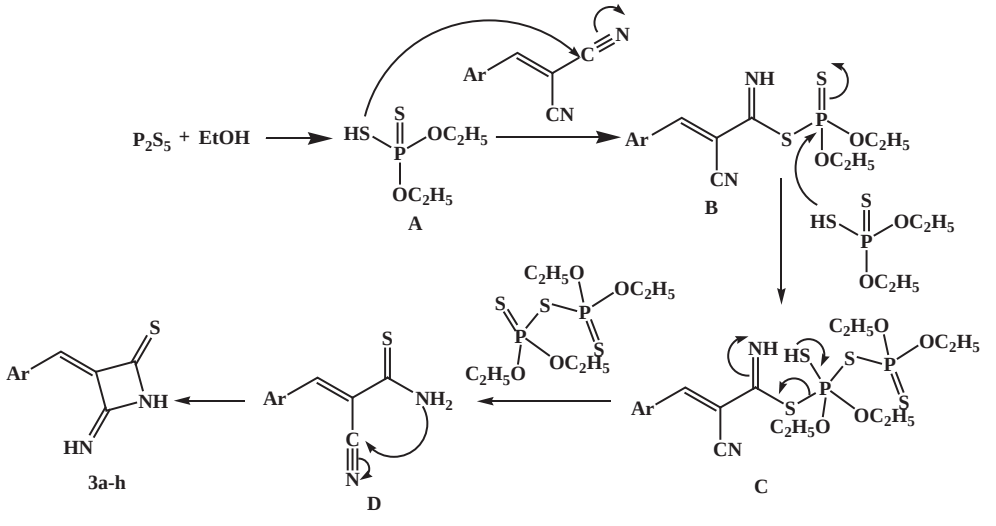
Commercially available phosphorus pentasulfide has been widely employed in organic synthesis for effecting the conversion of carbonyl compounds to thiocarbonyl compounds under a variety of conditions such as the use of polar solvents or base catalysts.[19–21] Despite the wide range of reagents available for the conversion of nitriles to thioamides,[22] little attempts have been made to use the readily accessible phosphorus pentasulfide. Recently simply phosphorus pentasulfide in different solvents, especially in ethanol under refluxing conditions, has been reported to give thioamides.[23] In this paper, we wish to provide an efficient single-step procedure for the preparation of 4-imino-3-(arylidene)-azetidine-2-thiones from arylidenemalononitriles with P_2S_5 in ethanol.

As shown in Scheme 1, the reaction of arylidenemalononitriles **2a–h** with phosphorus pentasulfide in refluxing ethanol, afforded azetidine-2-thiones **3a–h** in good yields. The arylidenemalononitriles **2a–h** were prepared from the reaction of arylaldehydes **1a–h** with malonitrile in ethanol under reflux in the presence of phosphorus pentoxide as catalyst.

The structures of compounds **3a–h** were deduced from their elemental analyses and their infrared (IR), ^{1}H NMR and ^{13}C NMR spectra.



Scheme 1. Synthesis of 4-imino-3-(arylidene)-azetidine-2-thiones **3a-h**.



Scheme 2. A plausible mechanism for the synthesis of azetidine-2-thiones **3a–h**.

For example, the ^{1}H NMR spectrum of **3b** exhibited two broad signals at $\delta = 9.46$ and 9.97 ppm, respectively, due to the NH protons and a signal at 8.04 ppm for the vinylic proton. The two single signals observed at 9.46 and 9.97 ppm disappeared after the addition of a few drops of D_2O to DMSO-d_6 solution of compound **3b**. These signals are related to NH protons.

A plausible mechanism for the formation of azetidine-2-thiones **3a–h** is proposed as shown in Scheme 2. First, P_2S_5 reacts with ethanol to furnish the activated intermediate O,O-diethyl S-hydrogen phosphorodithioate **A**. Nucleophilic attack on arylidenemalononitriles by **A** provides the intermediate **B**, which reacted with the same active specie of **A** to afford the thioamide **D**, with the elimination of phosphorus oxide-sulfide. Azetidine-2-thiones **3a–h** cores were formed by means of subsequent intramolecular cyclization of **D**.

3. Conclusions

In summary, with a simple approach, a new series of 4-imino-3-(arylidene)-azetidine-2-thiones **3a–h** were synthesized by reaction of arylidenemalononitriles with P_2S_5 in the presence of ethanol. This appears to be a new method to prepare new building blocks of possible interest in medicinal chemistry. Compounds **3a–h** can be used as intermediates and synthons for the construction of several interesting heterocyclic compounds.

4. Experimental

Melting points were determined using a Büchi-Tottoli apparatus. IR spectra were recorded on a Perkin-Elmer 577 spectrometer using KBr disks; only noteworthy IR absorptions are listed (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, DMSO-d_6 and solution (unless otherwise specified) with TMS as an internal reference using a Bruker AC 300 (^{1}H) or 75 MHz (^{13}C) instruments. Chemical shifts are given in d parts per million (ppm) downfield from TMS. Multiplicities of ^{13}C NMR resources were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. Low-resolution mass spectra (MS) were recorded on a Perkin-Elmer Sciex API 3000 spectrometer. Column chromatography was carried out on SiO_2 (silica gel 60 Merck 0.063–0.200 mm). Thin-layer chromatography (TLC) was carried out on SiO_2 (silica gel 60, F 254 Merck 0.063–0.200 mm), and the spots were located with UV light. Commercial reagents were used without further purification unless stated.

4.1. *General procedure for the synthesis of 2-(arylidene)malononitriles 2a–h*

In a 250 ml round bottom flask, aromatic aldehyde (10 mmol), malononitrile (10 mmol) and phosphorus pentoxide (3.54 mmol) were stirred mechanically for 10 min in 25 ml absolute ethanol. The resulting reaction mixture was heated at reflux using a water bath. The reaction mixture was poured on the crushed ice after the completion of the reaction monitored by TLC. On stirring, the separation of desired product takes place. The solid was filtered, washed with petroleum ether, dried and recrystalized by using ethanol.

4.1.1. *2-(Benzylidene)malononitrile (**2a**)*

Yield: 89%, Mp: 88–90°C; ^{1}H NMR (DMSO-d_6): δ 7.57–7.68 (m, 3H, H-Ar), 7.91–7.95 (m, 2H, H-Ar), 8.52 (s, 1H, H-vinyl); ^{13}C NMR (DMSO-d_6): δ 82.1 (C), 113.7 (CN), 114.6 (CN), 129.9 (2CH), 131.0 (2CH), 131.8 (C), 134.8 (CH), 162.0 (CHvinyl).

4.1.2. *2-(4-Methoxybenzylidene)malononitrile (**2b**)*

Yield: 86%, Mp: 110–112°C; ^{1}H NMR (DMSO-d_6): δ 3.86 (s, 3H, CH_3O), 7.14 (d, 2H, J = 9.0 Hz), 7.93 (d, 2H, J = 9.0 Hz), 8.34 (s, 1H, H-vinyl); ^{13}C NMR (DMSO-d_6): δ 56.4 (CH_3O), 77.3 (C), 114.3 (CN), 115.2 (CN), 115.6 (2CH), 124.6 (C), 133.8 (2CH), 160.9 (CHvinyl), 164.8 (=CO).

4.1.3. *2-(3-Methoxybenzylidene)malononitrile (**2c**)*

Yield: 88%, Mp: 134–136°C; ^{1}H NMR (DMSO-d_6): δ 3.79 (s, 3H, CH_3O), 7.24–7.28 (m, 1H, H-Ar), 7.49–7.52 (m, 3H, H-Ar),, 8.48 (s, 1H, H-vinyl); ^{13}C NMR (DMSO-d_6): δ 55.9 (CH_3O), 82.3 (C), 113.6 (CN), 114.5 (CN), 115.6 (CH), 120.7 (CH), 123.4 (CH), 131.2 (CH), 132.9 (C), 159.9 (=CO), 161.8 (CHvinyl).

4.1.4. *2-(2-Nitrobenzylidene)malononitrile (**2d**)*

Yield: 90%, Mp: 124–126°C; ^{1}H NMR (DMSO-d_6): δ 7.87–8.00 (m, 3H, H-Ar), 8.32 (dd, 1H, J = 8.1 et 1.2 Hz), 8.95 (s, 1H, H-vinyl); ^{13}C NMR (DMSO-d_6): δ 87.5 (C), 112.3 (CN), 113.6 (CN), 125.9 (CH), 127.6 (C), 130.9 (CH), 133.8 (CH), 135.5 (CH), 147.3 (C), 161.8 (CHvinyl).

4.1.5. *2-(4-Chlorobenzylidene)malononitrile (**2e**)*

Yield: 79%, Mp: 148–150°C; ^{1}H NMR (DMSO-d_6): δ 7.67 (d, 2H, J = 8.4 Hz), 7.92 (d, 2H, J = 8.4 Hz), 8.51 (s, 1H, H-vinyl); ^{13}C NMR (DMSO-d_6): δ 82.7 (C), 113.5 (CN), 114.5 (CN), 130.2 (2CH), 130.6 (C), 132.6 (2CH), 139.5 (C), 160.6 (CHvinyl).

4.1.6. *2-(3-Bromobenzylidene)malononitrile (**2f**)*

Yield: 69%, Mp: 112–114°C; ^{1}H NMR (DMSO-d_6): δ 7.56 (t, 1H, J = 8.1 Hz), 7.85–7.94 (m, 2H, H-Ar), 8.08 (m, 1H, H-Ar),, 8.50 (s, 1H, H-vinyl); ^{13}C NMR (DMSO-d_6): δ 84.0 (C), 113.2 (CN), 114.3 (CN), 122.8 (C), 129.4 (CH), 132.0 (CH), 133.3 (CH), 133.8 (C), 136.9 (CH), 160.3 (CHvinyl).

4.1.7. *2-(4-Methylbenzylidene)malononitrile (**2g**)*

Yield: 68%, Mp: 130–132°C; ^{1}H NMR (DMSO-d_6): δ 2.39 (s, 3H, CH_3), 7.41 (d, 2H, J = 8.1 Hz), 7.84 (d, 2H, J = 8.1 Hz), 8.45 (s, 1H, H-vinyl); ^{13}C NMR (DMSO-d_6): δ 21.9 (CH_3), 80.4 (C), 113.9 (CN), 114.8 (CN), 129.2 (C), 130.6 (2CH), 131.1 (2CH), 146.1 (C), 161.8 (CHvinyl).

4.1.8. *2-(4-(Dimethylamino)benzylidene)malononitrile (**2h**)*

Yield: 96%, Mp: 172–174°C; ^{1}H NMR (DMSO-d_6): δ 3.08 (s, 3H, $N(CH_3)_2$), 6.81 (d, 2H, J = 9.3 Hz), 7.79 (d, 2H, J = 9.3 Hz), 7.99 (s, 1H, H-vinyl); ^{13}C NMR (DMSO-d_6): δ 40.1 (NCH_3), 69.1 (C), 112.2 (2CH), 115.9 (CN), 116.7 (CN), 119.2 (C), 134.1 (2CH), 154.8 (C), 159.3 (CHvinyl).

4.2. *General procedure for the synthesis of 4-Imino-3-(arylidene)-azetidine-2-thiones 3a–h*

A solution of phosphorus pentasulfide P_2S_5 (20 mmol) in ethanol absolute (10 mL) was stirred for 1 h. Arylidenemalononitrile (10 mmol) was added and the resulting solution was heated to reflux for 3–6 h. The mixture was then washed with ethyl acetate; the organic phase was dried over $MgSO_4$ and concentrated in vacuo. Chromatography (EtOAc–hexane 10:90) gave the pure azetidine-2-thiones in good yield.

4.2.1. *4-Imino-3-(benzylidene)-azetidine-2-thione (**3a**)*

Yield:50%, Mp: 135–137°C; IR (KBr, cm^{-1}): 3310, 3180 (2NH), 1590 (C=NH), 1210 (CS); ^{1}H NMR (DMSO-d_6): δ 7.30–7.36 (m, 3H, H-Ar), 7.51–7.55 (m, 2H, H-Ar), 8.06 (s, 1H, H-vinyl), 9.71 (s, 1H, NH), 9.86 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 128.5 (CH), 116.7 (C), 119.2 (C), 129.1 (CH), 129.7 (CH), 130.6 (CH), 132.7 (CH), 133.9 (C), 147.2 (CHvinyl), 192.8 (CS); MS: m/z 189 $[M + 1]^+$. Anal. Calcd for $C_{10}H_8N_2S$: C, 63.80; H, 4.28; N, 14.88. Found: C, 63.72; H, 4.36; N, 14.75.

4.2.2. *4-Imino-3-(4-methoxybenzylidene)-azetidine-2-thione (**3b**)*

Yield: 78%, Mp: 191–193°C; IR (KBr, cm^{-1}): 3300, 3170 (2NH), 1605 (C=NH), 1180 (CS); ^{1}H NMR (DMSO-d_6): δ 3.83 (s, 3H, CH_3O), 7.11 (d, 2H, $J = 9.0$ Hz), 7.94 (d, 2H, $J = 9.0$ Hz), 8.04 (s, 1H, H-vinyl), 9.46 (s, 1H, NH), 9.97 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 56.1 (CH_3O), 109.5 (C), 115.4 (2CH), 117.3 (C), 124.6 (C), 133.2 (2CH), 147.5 (CHvinyl), 163.1 (=CO), 193.1 (CS); MS: m/z 219 $[M + 1]^+$. Anal. Calcd for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83. Found: C, 60.65; H, 4.51; N, 12.74.

4.2.3. *4-Imino-3-(3-methoxybenzylidene)-azetidine-2-thione (**3c**)*

Yield: 86%, Mp: 136–138°C; IR (KBr, cm^{-1}): 3270, 3140 (2NH), 1615 (C=NH), 1195 (CS); ^{1}H NMR (DMSO-d_6): δ 3.79 (s, 3H, CH_3O), 7.12–7.16 (m, 1H, H-Ar), 7.46–7.51 (m, 3H, H-Ar), 8.02 (s, 1H, H-vinyl), 9.61 (s, 1H, NH), 10.10 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 55.8 (CH_3O), 113.1 (C), 115.3 (CH), 116.7 (C), 118.6 (CH), 123.2 (CH), 130.8 (CH), 133.6 (C), 147.1 (CHvinyl), 159.9 (=CO), 192.8 (CS); MS: m/z 219 $[M + 1]^+$. Anal. Calcd for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83. Found: C, 60.58; H, 4.56; N, 12.68.

4.2.4. *4-Imino-3-(2-nitrobenzylidene)-azetidine-2-thione (**3d**)*

Yield: 56%, Mp: 109–111°C; IR (KBr, cm^{-1}): 3280, 3165 (2NH), 1600 (C=NH), 1510, 1365 (NO_2), 1185 (CS); ^{1}H NMR (DMSO-d_6): δ 7.77–7.85 (m, 2H, H-Ar), 7.90–7.95 (m, 1H, H-Ar), 8.26 (d, 1H, $J = 8.1$ Hz), 8.47 (s, 1H, H-vinyl), 9.63 (s, 1H, NH), 10.24 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 55.8 (CH_3O), 115.4 (C), 117.1 (C), 125.7 (CH), 129.1 (C), 131.2 (CH), 132.4 (CH), 135.2 (CH), 146.6 (CHvinyl), 147.6 (=CN), 191.1 (CS); MS: m/z 234 $[M + 1]^+$. Anal. Calcd for $C_{10}H_7N_3O_2S$: C, 51.49; H, 3.02; N, 18.02. Found: C, 51.62; H, 3.14; N, 17.94.

4.2.5. *4-Imino-3-(4-chlorobenzylidene)-azetidine-2-thione (**3e**)*

Yield: 58%, Mp: 185–186°C; IR (KBr, cm^{-1}): 3320, 3150 (2NH), 1600 (C=NH), 1200 (CS); ^{1}H NMR (DMSO-d_6): δ 7.61 (d, 2H, $J = 9.3$ Hz), 7.92 (d, 2H, $J = 9.3$ Hz), 8.15 (s, 1H, H-vinyl), 9.00 (s, 1H, NH), 9.50 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 107.8 (C), 129.8 (2CH), 131.2 (C),

132.1 (2CH), 137.3 (C), 149.7 (CHvinyl), 160.1 (C), 192.0 (CS); MS: m/z 223 $[M + 1]^+$. Anal. Calcd for $C_{10}H_7ClN_2S$: C, 53.93; H, 3.17; N, 12.58. Found: C, 54.12; H, 3.35; N, 12.46.

4.2.6. *4-Imino-3-(3-bromobenzylidene)-azetidine-2-thione (**3f**)*

Yield: 45%, Mp: 173–174°C; IR (KBr, cm^{-1}): 3275, 3150 (2NH), 1605 (C=NH), 1200 (CS); ^1H NMR (DMSO-d_6): δ 7.77–7.95 (m, 3H, H-Ar), 8.26 (dd, 1H, $J = 8.1$ and 1.2 Hz), 8.47 (s, 1H, H-vinyl), 9.62 (s, 1H, NH), 10.24 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 115.4 (C), 117.1 (C), 125.7 (CH), 129.1 (C), 131.2 (CH), 132.4 (CH), 135.2 (CH), 146.7 (CHvinyl), 147.6 (C), 191.1 (CS); MS: m/z 268 $[M + 1]^+$, 270 $[M+3]^+$. Anal. Calcd for $C_{10}H_7BrN_2S$: C, 44.96; H, 2.64; N, 10.49. Found: C, 44.84; H, 2.56; N, 10.57.

4.2.7. *4-Imino-3-(4-methylbenzylidene)-azetidine-2-thione (**3g**)*

Yield: 62%, Mp: 168–170°C; IR (KBr, cm^{-1}): 3280, 3165 (2NH), 1610 (C=NH), 1190 (CS); ^1H NMR (DMSO-d_6): δ 2.36 (s, 3H, CH_3), 7.35 (d, 2H, $J = 8.1$ Hz), 7.82 (d, 2H, $J = 8.1$ Hz), 8.03 (s, 1H, H-vinyl), 9.56 (s, 1H, NH), 10.05 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 21.7 (CH_3), 111.7 (C), 116.9 (C), 129.6 (C),130.4 (2CH), 130.8 (2CH), 143.4 (C), 147.4 (CHvinyl), 192.9 (CS); MS: m/z 203 $[M+1]^+$. Anal. Calcd for $C_{11}H_{10}N_2S$: C, 65.32; H, 4.98; N, 13.85. Found: C, 65.45; H, 5.08; N, 13.70.

4.2.8. *4-Imino-3-(4-(dimethylamino)benzylidene)-azetidine-2-thione (**3h**)*

Yield: 89%, mp: 236–238°C; IR (KBr, cm^{-1}): 3285, 3180 (2NH), 1600 (C=NH), 1205 (CS); ^1H NMR (DMSO-d_6): δ 3.04 (s, 3H, NCH_3), 6.80 (d, 2H, $J = 9.0$ Hz), 7.85 (d, 2H, $J = 9.0$ Hz), 8.04 (s, 1H, H-vinyl), 9.12 (s, 1H, NH), 9.67 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 40.0 (NCH_3), 103.8 (C), 112.3 (2CH), 118.5 (C), 118.8 (C), 133.7 (2CH), 153.6 (C), 149.2 (CHvinyl), 193.4 (CS); MS: m/z 232 $[M + 1]^+$. Anal. Calcd for $C_{12}H_{13}N_3S$: C, 62.31; H, 5.66; N, 18.17. Found: C, 62.48; H, 5.58; N, 18.24.

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Supplemental data

Supplemental data for this article can be accessed at 10.1080/17415993.2014.956213.

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