



Original Research Article

Rapid access of some rare chiral azides from sterically hindered alcohols by green chemistry protocol

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KEYWORDS

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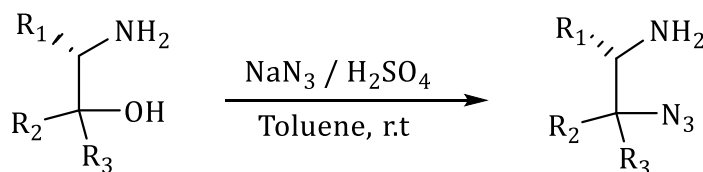
Enantioselective Reaction

Dean-Stark trap

ABSTRACT

Azides are the precursors of two important derivatives in the synthetic organic chemistry. Achiral amines are not as demandable as that of chiral ones. Chiral amines and diamines have versatile uses in enantioselective reactions. Both simple and amino alcohols were undergone smooth azidation reaction in the mixture of NaN_3 and H_2SO_4 in toluene solvent and afforded good to charming yields. Importantly, optical purity of some chiral amino alcohols was reserved during azidation reaction. This is an efficient method to synthesize new azides for the fabrication of new organocatalyst which is friendly to the environment.

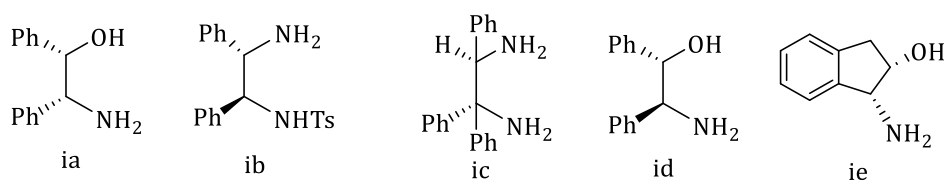
Graphical Abstract



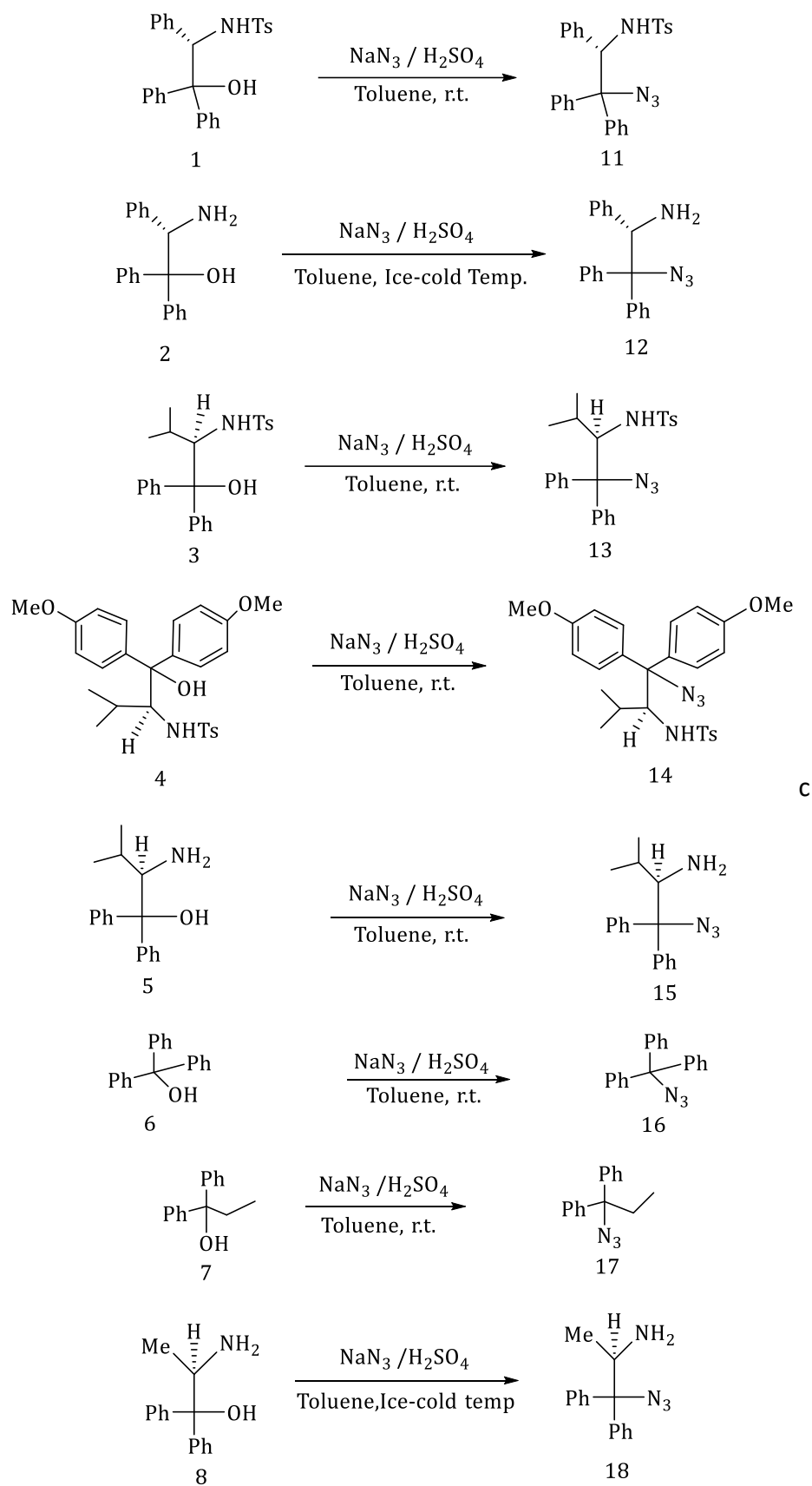
Introduction

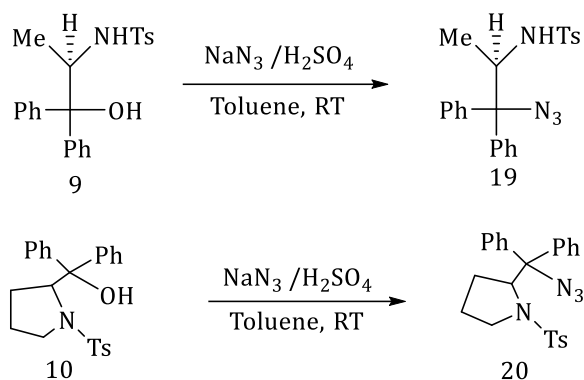
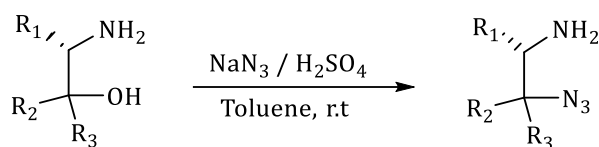
Azides are important precursors of nitrenes [1, 2] and amino compounds [3, 4] and are frequently used as 1,3-dipoles for cycloaddition [5] with alkenes. Besides, azides are the chief sources of 1,2-amino alcohols and 1,2-diamino compounds or its derivatives. All these are valuable chiral building blocks [6] for asymmetric synthesis and are acting as organocatalysts [7–9]. Notably, in recent years, beta-amino alcohols with various structures are successfully being used as chiral auxiliaries [10, 11] in different enantioselective reactions, e.g., (Reductions, nucleophilic addition to the carbonyl groups, Prins reaction and Diels'-Alder reaction). Recently developed Ru/Rh complexes with chiral 1,2-diamines or their derivatives (Scheme 1) have proved to be potentials for the asymmetric transfer of hydrogen [12] in constructing enantiomerically enriched alcohols.

So, keeping eyes on the vast uses of amines and diamines, several methods have emerged to make newer & newer azides. TFA with NaN_3 [13], NaN_3 in DMF [14, 15] and the Mitsunobu azidation [16] methods are the notable examples. Versatile applicability of chiral diamines also envisaged us to take an initiative to synthesize azide **11** from alcohol **1** (Scheme 2) by NaN_3 and trifluoro acetic acid (TFA) in chloroform solvent, but we could not get success to obtain the product **11**. Some workers have successfully replaced azide group in the place of -OH for few amino alcohols by diethyl or diisopropyl azodicarboxylate (DEAD)/DIAD), PPh_3 and HN_3 treatment [17, 18]. We followed all these methods to get the target azide **11**, but we were unsuccessful. In each case, only starting materials were recovered. This may be the steric grounds for which the replacement of -OH by $-\text{N}_3$ functionality was difficult. All these efforts therefore made us puzzled and envisaged us to rethink about the matter. As a result, naturally, we welcomed recently developed zeolite method by Sreekumar et al. [19–21] in which azidation reaction was carried out in H-Y zeolite incorporated with NaN_3 . We also followed the same method but unfortunately, we did not obtain azide **11** from alcohol **1**. We think it may be happened due to the mismatching of sizes between the substrate and the pores of zeolites. After successive failures, we have tried to exploit a cheap and available electrophilic source for the direct displacement of -OH as H_2O by $-\text{N}_3$ functionality. Therefore, we have reported, here, a very simple method using NaN_3 and H_2SO_4 in toluene solvent for the azidation of sterically hindered alcohols (Scheme 3).



Scheme 1.



**Scheme 2.****Scheme 3.**

Experimental

Materials and methods

The melting points were determined on a capillary melting point apparatus and are uncorrected. Infrared spectra were recorded using KBr pellets for solids and neat for liquids on FT-IR 8400 PerkinElmer 883 grating spectrometer. ¹H NMR and ¹³C NMR spectra were taken on AC-Bruker 200 MHz spectrometer in D₆-DMSO, containing TMS as internal standard. All *J* values are given in Hz, chemical shifts in δ -units. Reactions were monitored by TLC and column chromatography and were carried out on 60-120 mesh E. Merck silica gel and, also, the substrates were purchased from Fluka chemicals.

General Procedure for azide synthesis

Vacuum dried NaN₃ (73 mg, 1.128 mmol) was taken into a two necked RB flask and anhydrous toluene (12 mL) was added *via* syringe. Concentrated H₂SO₄ (0.1 mL, 10 equiv, 98%, d=1.84) was slowly added to it and, then, the mixture was stirred at about 15 minute at room temperature. Highly vacuum dried alcohol **1** (100 mg, 0.226 mmol) was then quickly to it and the resulting reaction mixture was shaken vigorously (Sometimes by hand) at about one minute. Rapid quenching with cold water (10 mL) gave two distinct layers. Organic layer was separated and the water layer was extracted by EtOAc (2×15 mL). The organic extracts were combined anhydrous Na₂SO₄ was dried

over and, finally, the concentration afforded a crude mass. Column chromatography with the crude mass by *n*-hexane/ethyl acetate (9:1) gave the pure product **11** in 56% (60 mg) yield.

For compound 11

White solid, mp 193–194 °C, IR (KBr) (ν_{\max} / cm^{-1}): 2101 (N_3) and 3287. ^1H (CDCl_3 , 300 MHz): δ 7.38–7.31 (m, 5H, Ar-H), 7.22–7.13 (m, 8H, Ar-H), 6.95 (t, 1H, $J = 7.5$), 6.86–6.76 (m, 3H, Ar-H), 6.46 (d, 2H, $J = 7.5$, Ar-H), 4.44 (d, 1H, $J = 9.6$), 5.03 (d, 1H, $J = 9.6$), 2.23 (s, 3H, $-\text{CH}_3$). ^{13}C NMR (CDCl_3 , 75 MHz): δ 142.7, 139.8, 138.7, 137, 135, 128.8 (3C), 128.8 (3C), 128.3, 128.3 (4C), 128 (2C), 127.9, 127.1, 127 (2C), 126.9 (2C), 75.5, 62.2, 21.2. MS; 468 (0.01%), 426 (0.99%, $-\text{N}_3$), 260 (100%), 180 (76.70%), 154 (84.62%), 91 (73.42%), 77 (46.73%). Optical rotation at 27.2 °C, -25.74° (c, 0.545, CHCl_3).

For compound 12

Yield 57 mg (52.5%), IR (KBr) (ν_{\max} / cm^{-1}): 2103. ^1H NMR (CDCl_3 , 300 MHz): δ 7.39–7.29 (m, 5H, Ar-H), 7.23–7.10 (m, 8H, Ar-H), 7.07–6.95 (m, 2H, Ar-H), 5.05 (s, 1H), 1.73 (brs, 2H, $-\text{NH}_2$). ^{13}C NMR (CDCl_3 , 75 MHz): δ 140.9, 140.1, 139.5, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.5, 127.5, 127.3, 127.2, 127.2, 127, 126.8, 76.3, 62.6. MS; 315 (55%), 251 (5.67%), 180.1 (39.72%), 105.9 (100%), 77 (18.49%). Optical rotation at 28 °C, -86.78° (c, 0.545, CHCl_3).

For compound 13

White solid, yield 31 mg (58%), mp 157–158 °C, IR (KBr) (ν_{\max} / cm^{-1}): 2103 and 3187. ^1H NMR (CDCl_3 , 300 MHz): δ 7.59 (d, 2H, $J = 8$, Ar-H), 7.33–7.24 (m, 10H, Ar-H), 7.18 (d, 2H, $J = 8$, Ar-H), 4.47 (d, 1H, $J = 11$), 4.32 (d, 1H, $J = 11$, $-\text{OH}$), 2.37 (s, 3H, Ar- CH_3), 2.08–2.04 (m, 1H), 1.06 (d, 3H, $J = 6.9$, $-\text{CH}_3$), 0.42 (d, 3H, $J = 6.9$, $-\text{CH}_3$). ^{13}C NMR (CDCl_3 , 75 MHz): δ 142.7, 139.7, 138.9, 138.7, 129.2 (2C), 128.3 (2C), 128.3 (2C), 128 (3C), 127.9, 126.6 (2C), 126.7 (2C), 76.5, 63.1, 28.5, 22.8, 21.4, 16.7. Optical rotation at 20.7 °C, -8.68° (c, 0.535, CHCl_3).

For compound 14

White solid, Yield 73 mg (69%), mp 169–170 °C, IR (KBr) (ν_{\max} / cm^{-1}): 2103 ($-\text{N}_3$). ^1H NMR (CDCl_3 , 300 MHz): δ 7.61 (d, 2H, $J = 8$, Ar-H), 7.29–7.14 (m, 6H, Ar-H), 6.84–6.79 (m, 4H, Ar-H), 4.29 (q, 2H, $J = 12$), 3.80 (s, 3H), 3.79 (s, 3H, Ar- CH_3), 2.39 (s, 3H, Ar- CH_3), 2.06–2.01 (m, 1H), 1.05 (d, 3H, $J = 6.9$), 0.39 (d, 3H, $J = 6.9$). ^{13}C NMR (CDCl_3 , 75 MHz): δ 159.2, 159, 142.7, 138.9, 131.8, 130.9, 129.4 (2C), 129.2 (3C), 128.9 (2C), 126.7 (3C), 113.6 (2C), 75.9, 63.4, 55.2, 55.1, 28.5, 22.9, 21.4, 16.9. MS; 452.1 (not found MW, expulsion of $-\text{N}_3$ group), 408.1, 296.2, 253.1, 240.1, 226.1, 210.1, 197.1, 154.9, 134.0, 120.9, 91.0, 77.0, 65. Optical rotation at 25.3 °C, -8.22° (c, 0.515, CHCl_3).

For compound 15

White solid, yield 58 mg (53%), mp 97–98 °C, IR (KBr) (ν_{\max} / cm^{-1}): 2103. ^1H NMR (CDCl_3 , 300 MHz): δ 7.46–7.35 (m, 5H, Ar-H), 7.33–7.23 (m, 5H, Ar-H), 3.77 (brs, 1H), 1.84–1.79 (m, 1H), 1.34 (brs, 2H, $-\text{NH}_2$), 1.02 (d, 3H, $J = 9$, $-\text{CH}_3$), 0.58 (d, 3H, $J = 9$, $-\text{CH}_3$). ^{13}C NMR (CDCl_3 , 75 MHz): δ 141.3, 141, 128.4, 128.3, 128, 127.8, 127.5, 127.3, 127.2, 76.9, 61.4, 27.7, 23.3, 15.5. MS; 281.1 (0.77%), 251 (3.79%), 194.1 (8.48%), 180 (87.78%), 103.72 (26.54%), 72 (100%). Optical rotation at 20.2 °C, -38.17° (c, 0.543, CHCl_3).

For compound 16

Neat liquid, yield 143 mg (87%), IR (KBr) (ν_{\max} / cm^{-1}): 2103. ^1H NMR (CDCl_3 , 300 MHz): δ 7.37–7.25 (m, 15H, Ar-H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 143.3, 143, 142.8, 128.7, 128.6, 128.4 (3C), 128.3 (3C), 128.1, 128, 127.7, 127.6, 127.3 (2C), 126.8, 29.3. MS; 285 (0.30%), 243 (100%), 180 (43.37%), 165 (77.43%), 77 (59.72%).

For compound 17

White liquid, yield 61 mg (60.6%), IR (KBr) (ν_{\max} / cm^{-1}): 2101. ^1H NMR (CDCl_3 , 300 MHz): δ 7.35 (m, 10H, Ar-H), 2.43 (q, 2H, $J = 6$, $-\text{CH}_2$), 0.83 (t, 3H, $J = 6$, $-\text{CH}_3$); ^{13}C NMR (CDCl_3 , 75MHz): δ 142.9 (2C), 128.2 (4C), 127.3 (2C), 127.1 (4C), 73, 31.5, 8.5. MS; 253.1 (0.82%), 193.1, 180.1 (100%), 165.0, 152, 132, 105, 77.

For compound 18

White solid, Yield 13 mg (13%), mp 127–128 °C, IR (KBr) (ν_{\max} / cm^{-1}): 2103. ^1H NMR (CDCl_3 , 300 MHz): δ 8.20 (brs, 2H, $-\text{NH}_2$), 7.53–7.19 (m, 10H, Ar-H), 4.68–4.66 (m, 1H, ali-H), 1.00 (d, 3H, $J = 6$, $-\text{CH}_3$). ^{13}C NMR (75 MHz, CDCl_3): δ 146.9, 144.7, 128.3 (2C), 127.9 (2C), 126.6, 126.3, 125.8 (2C), 125.4 (2C), 78.4, 51.8, 17.1. MS; 253.1 (11.96%), 193.1, 183.1 (100%), 165, 152, 132, 105, 77. Optical rotation at 23 °C, -25.67° (c, 0.565, CHCl_3).

For compound 19

White solid, yield 59 mg (55%), mp 137–138 °C, IR (KBr) (ν_{\max} / cm^{-1}): 2103. ^1H NMR (CDCl_3 , 300 MHz): δ 7.65 (d, 2H, $J = 8.1$, Ar-H), 7.35–7.23 (m, 12H, Ar-H), 4.50–4.48 (m, 1H), 4.23–4.20 (m, 1H), 2.41 (s, 3H, Ar- CH_3), 1.1 (d, 3H, $J = 6$, C^*-CH_3). ^{13}C NMR (CDCl_3 , 75 MHz): δ 143.3, 139.1, 138.5, 138, 129.5, 128.3 (4C), 128.2 (2C), 128.1 (2C), 128, 127.8 (2C), 127 (2C), 75.6, 54.8, 21.4, 18.6. MS; 406 (0.01%), 364, 272, 198 (100%), 180, 154.9, 90, 77. Optical rotation at 23 °C, -12.57° (c, 0.565, CHCl_3).

For compound 20

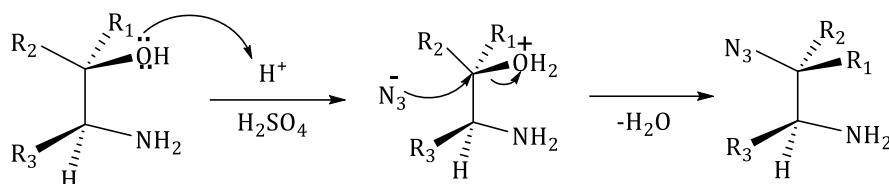
White solid, yield 37 mg (69%), mp 157–158 °C, IR (KBr) (ν_{max} / cm^{-1}): 2104. ^1H NMR (CDCl_3 , 300 MHz): δ 7.68 (d, 2H, $J = 8.2$), 7.41–7.34 (m, 4H, Ar-H), 7.31–7.23 (m, 8H, Ar-H), 5.22–5.18 (m, 1H, ring-H), 3.44–3.31 (m, 2H, ring-H), 2.43 (s, 3H, Ar-Me), 2.42–2.35 (m, 2H, ring-H), 1.91–1.87 (m, 2H, ring-H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 143.2, 140, 139.1, 136.6, 129.4 (2C), 129 (2C), 128.5 (2C), 128.1, 128.1, 127.9, 127.6, 127.5, 127.5, 127.3, 127.2, 79.7, 67.2, 49.9, 29.6, 23.7, 21.56. MS; 432.2 (0.01%), 224.1 (100%), 155 (8.75%). Optical rotation at 18.7 °C, -120° (c, 0.563, CHCl_3).

Results and discussion

At the very beginning, 50 mg of the starting alcohol **1** was taken in anhydrous toluene and, then, the vacuum dried NaN_3 was added to it. Dean-Stark trap was set to remove the water formed during the reaction. In TLC, several spots were observed from which azide **11** (Less than 7%) was isolated. Rearranged and fragmented products were formed from the newly born azide due to its' long exposure in strong acidic reaction conditions. To improve the yield of the azide **11**, and to overcome the reaction difficulties, we slightly changed the reaction technique. Highly vacuum dried NaN_3 (5 equiv.) was placed in bulk anhydrous toluene and then the concentrated H_2SO_4 (10 equiv.) was added to it. It was stirred at about 15 minute to ensure the formation of HN_3 acid in the solution. After that, the dried alcohol **1** was quickly added to it and the resulting reaction mixture was vigorously shaken for one minute. To stop the reaction, cold water was added and by that tricky way the most reacting species proton was separated from the newly formed azide.

Thus, we were able to to minimize the destruction of newly born azide and got the improved result. In IR spectroscopy, a strong, sharp peak was observed at 2101 cm^{-1} for $-\text{N}_3$ functionality. Several other spectroscopic data were taken which proved unambiguous settlement of azides in the place of -OH. By this simple and one subtle step we have synthesized ten different sterically hindered azides with good to charming yields (Scheme 2). Next, in order to test the efficacy of our method, we imposed this technique onto some amino alcohols. Here, azidations are also going on smoothly by the addition of alcohols to $\text{NaN}_3/\text{H}_2\text{SO}_4$ solution at ice cold temperature. Later on, we have measured optical rotations for some of the chiral azides, and interestingly, we found optical rotations with some reasonable values.

Plausible mechanism of this simple reaction could be depicted by the following manner (Scheme 4).

Scheme 4.

The important advantage of this protocol is that it is going smoothly for the amino alcohols without any protection. But, the protected amino alcohols reaction should stop within 5~10 minute, unless, some elimination products will be resulted.

Conclusion

In conclusion, it can be stated that by this simple, quick, and non pollutant method we can readily obtain some sterically hindered azides in moderate to charming yields. Moreover, optical purity of the chiral azides were reserved, which is essential for making chiral auxiliaries.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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