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Conjugation and cyclization—two strong driving forces leading to the formation of new chromophores

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ABSTRACT

Novel chromophores formed in the solvent reactions of α-amino acids and small peptides were identified by crystal structure analysis and characterized by UV absorption. The formation of these chromophores in basic solutions was attributed to two strong driving forces—conjugation and cyclization. The discussion of possible reaction pathways could benefit the future design of α-amino acid-based chromophores.

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In our early research on the trifluoroethylation of α-amino acids and small peptides, it was found that the trifluoroethylated N-termini of linear dipeptides retained sufficient nucleophilicity to undergo intramolecular cyclization reactions to form cyclic dipeptides (2,5-diketopiperazines, DKPs).[1] This stimulated us to explore the possibility of building N-trifluoroethylated linear peptide bonds, for example, by deprotonating the trifluoroethylated α-amino proton and using amino acid fluorides for the coupling reactions.[2] Further, by converting N^{α}-protected amino acids into the corresponding acid chlorides, we were eventually able to construct the N-1*H*,1*H*-perfluoroalkylated linear peptide bonds.[3]

In the modification of N-1*H*,1*H*-perfluoroalkylated α-amino acids and small peptides, several compounds that resulted from solvent reactions attracted our attention due to their unique structures. In the first example shown in Scheme 1, we attempted to replace the methoxy moiety of the N^{α}-pentafluoropropylated (L)phenylalanine methyl ester with methylene cyanide $-CH_2CN$ formed in situ by deprotonating the solvent acetonitrile.[4] Following the reaction with the N^{α}-phthaloyl-protected glycine acid chloride, the compound **1**(*R*,*S*) bearing a unique chromophore was obtained.[5,9] The crystal structure of **1**(*R*) is shown in Figure 1.

Compound **1**(*R*,*S*) contains a five-membered ring. Four of the five ring atoms are in a planar conjugated system containing 10π electrons, as shown in Figure 2.

To characterize the newly formed chromophore in compound **1**(*R*,*S*), UV spectra were obtained. The two starting α-amino acid derivatives (in acid form) were also subjected to UV measurement under the same conditions, as shown in Figure 3. The newly formed chromophore in compound **1**(*R*,*S*) has a $\lambda_{max} = 265$ nm and a molar extinction coefficient $\varepsilon_{max} = 3.46 \times 10^4$.

The proposed rationale for the formation of compound **1** is shown in Scheme 2. Solvent CH_3CN was deprotonated by NaH. The methylene cyanide attacked the carbonyl carbon of phenylalanine methyl ester to replace the methoxy moiety. Racemization at the α-carbon of (L)phenylalanine could occur at this stage. The racemic intermediate then underwent an intramolecular cyclization reaction to form a new five-membered ring intermediate. This cyclic intermediate was deprotonated at the methylene carbon of the ring resulting in the formation of a conjugated system containing 8π electrons. Subsequent reaction with N^{α}-phthaloyl glycine acid chloride converted the anionic intermediate into a neutral species. Through an intramolecular proton shift, the zwitterionic compound **1**(*R*,*S*) containing 10 conjugated π electrons was formed.

The second example of the formation of new chromophores from solvent reactions is shown in Scheme 3. In order to study the *N*/*O* selectivity toward the trifluoroethylating agent $CF_3CH_2I(C_6H_5)N(SO_2CF_3)_2$, deprotonation by NaH was expected to occur at the nitrogen of the secondary amide moiety of the starting cyclic dipeptide. However, when the deprotonation was carried out in DMF, both compound **2**(*R*,*S*) and compound **3**(*R*,*S*) were formed.[10–12]

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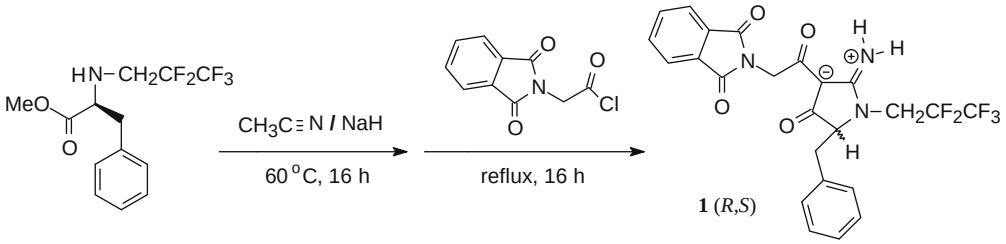


Scheme 1. The formation of compound **1**(*R*,*S*) (24%) bearing a unique chromophore.

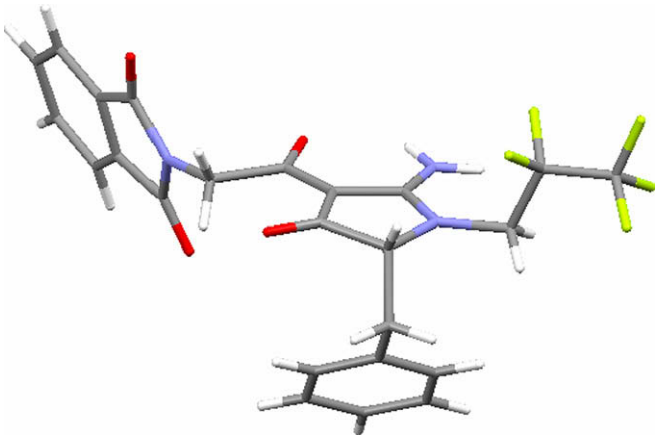


Figure 1. The crystal structure of compound **1**(*R*).

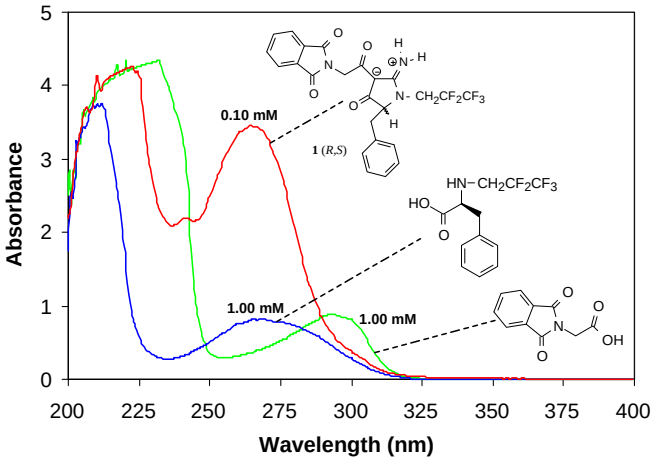


Figure 3. The solvent-subtracted UV absorption in EtOH of compound **1**(*R*,*S*) and the corresponding starting α-amino acid derivatives (acid form).

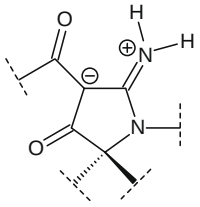


Figure 2. The novel chromophore of compound **1**(*R*,*S*).

The crystal structures of compound **2**(*S*) and compound **3**(*R*) are shown in Figure 4.

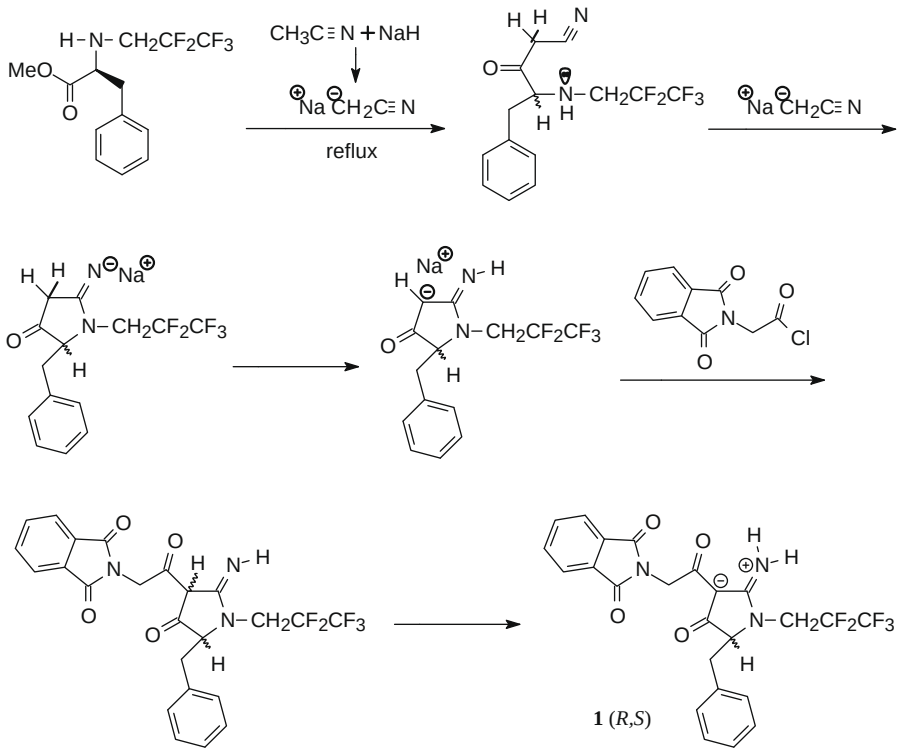
Compound **2**(*R*,*S*) contains a conjugated system with 10π electrons; while compound **3**(*R*,*S*) has a conjugated system with 14π electrons, as shown in Figure 5.

To characterize the newly formed chromophores in both compound **2**(*R*,*S*) and compound **3**(*R*,*S*), the UV measurements were carried out, as shown in Figure 6. The UV of the starting cyclic dipeptide was measured under the same conditions.

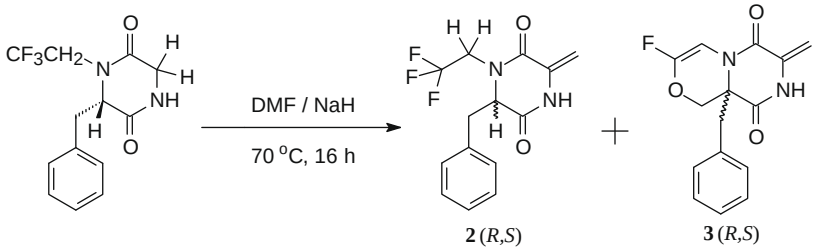
From Figure 6, it is clear that increasing the number of π electrons shifts the absorption wavelength toward the visible region (red shift).

The proposed rationale for the formation of compounds **2** and **3** is shown in Scheme 4. In the starting cyclic dipeptide N^{α}-CF_3CH_2(L)PheGly, three types of ring protons could be abstracted by NaH. However, only proton abstraction at the less sterically hindered ring methylene carbon first led to the irreversible C–C bond formation with solvent DMF to give the aldehyde intermediate. The conversion of the aldehyde intermediate into the alkoxide intermediate could occur via one of two pathways: (a) hydride acting as a nucleophile to attack the carbonyl carbon of the aldehyde;[13–18] or (b) homolytic cleavage of the carbonyl π bond, followed by (b1) a single electron transfer (SET) from hydride anion to the carbonyl oxygen radical and (b2) combination of the resulting H radical and carbonyl C radical to form the alkoxide intermediate.[19–24] The elimination of NaOH from the alkoxide intermediate gave compound **2**(*R*,*S*). The elimination of HF by NaH from the CF_3CH_2– moiety further extended the conjugated system. The irreversible C–C bond formation with solvent DMF in the presence of NaH at the more sterically hindered α-carbon of phenylalanine, followed by the conversion of aldehyde into alkoxide intermediate, provided a nucleophile. Intramolecular attack by alkoxide nucleophile on the difluoroenamine π bond and elimination of NaF resulted in a fused ring system, that is, compound **3**(*R*,*S*). Racemization at the α-carbon of the phenylalanine could occur in the first step.

In summary, the solvent CH_3CN or DMF reacted with an α-amino acid or a small peptide in the presence of NaH to form novel chromophores. The formation of these chromophores in basic solutions was attributed to two strong driving forces—conjugation and cyclization.



Scheme 2. The proposed rationale for the formation of compound **1**(*R*,*S*).



Scheme 3. The transformation of cyclic dipeptide N^{α}-CF_3CH_2(L)PheGly into compound **2**(*R*,*S*) (39%) and compound **3**(*R*,*S*) (46%) bearing novel chromophores.

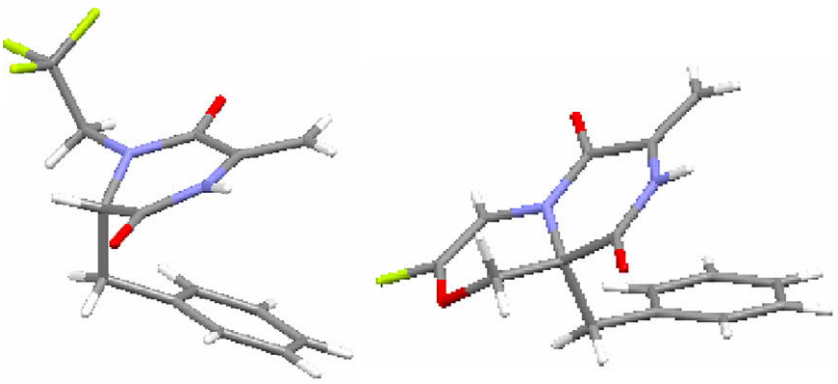


Figure 4. The crystal structures of compound **2**(*S*) (left) and compound **3**(*R*) (right).

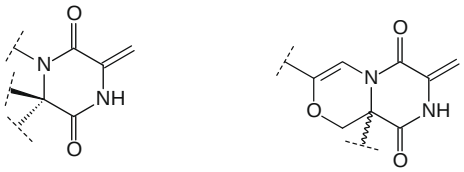


Figure 5. The chromophores of compound **2**(*R*,*S*) (left) and compound **3**(*R*,*S*) (right).

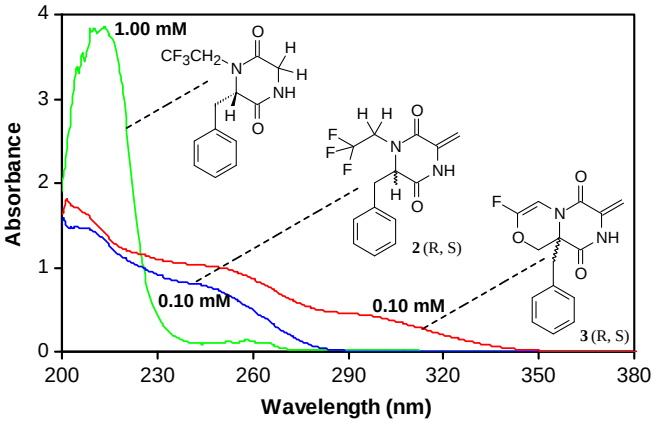
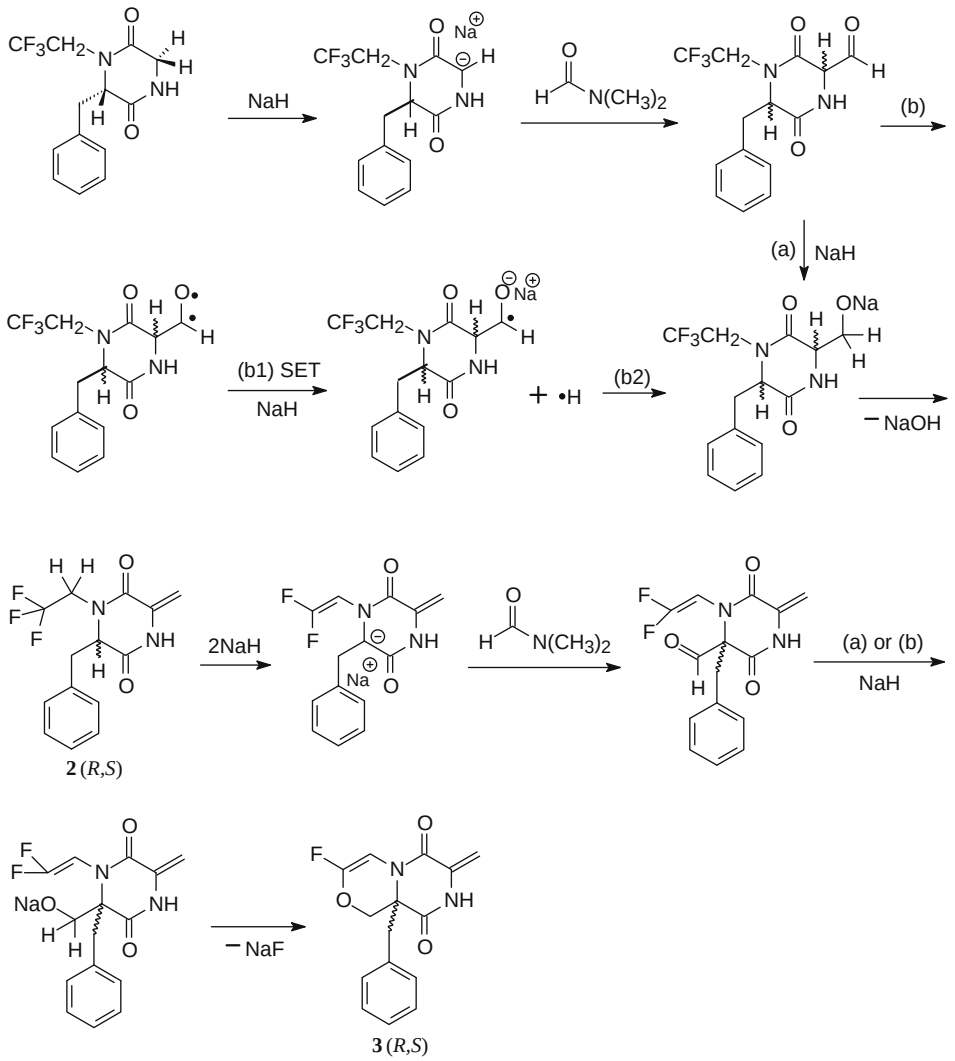


Figure 6. The solvent-subtracted UV absorption in EtOH of compound **2**(*R*,*S*) and compound **3**(*R*,*S*) along with the starting cyclic dipeptide.



Scheme 4. The proposed rationale for the formation of compound **2**(*R*,*S*) and compound **3**(*R*,*S*).

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.080.

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5. Preparation of **1**(*R*,*S*): N^{α}-$CF_3CF_2CH_2$(L)PheOMe[6] (0.933 g, 3.00 mmol) was dissolved in 10 mL of dry CH_3CN. NaH (95%, 0.197 g, 7.80 mmol) was wetted with 15 mL of dry CH_3CN. The N^{α}-$CF_3CF_2CH_2$(L)PheOMe solution was transferred into NaH/CH_3CN suspension. The reaction mixture was heated at 60 °C for 16 h. N^{α}-PhthGlyCl (0.805 g, 3.60 mmol)[7,8] was dissolved in 10 mL of dry CH_3CN. The obtained solution was transferred into N^{α}-$CF_3CF_2CH_2$(L)PheOMe/NaH/CH_3CN solution. The reaction mixture was refluxed for 16 h. The solvent was then evaporated. The resulting residue was partitioned between ethyl acetate and H_2O. The organic layer was separated and the solvent was evaporated. After column chromatography with 10–50% acetone in hexanes as eluent, **1**(*R*,*S*) was obtained (0.365 g, 0.719 mmol, 24.0%).
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9. Spectral data of **1**(*R*,*S*): ^{19}F NMR (282.78 MHz, acetone-d_6): δ −83.74 (3F, s), −118.2 to −118.4 (2F, octet). ^{1}H NMR (300.53 MHz, acetone-d_6): δ 3.16–3.44 (2H, m), 4.16–4.32 (1H, m), 4.25 (1H, dd), 4.58–4.74 (1H, m), 4.72–4.90 (2H, q), 7.18–7.38 (5H, m), 7.67 (1H, br s), 7.83–7.89 (4H, m), 8.67 (1H, br s). MS (ESI), MH^+, found 508.1122, $C_{24}H_{19}F_5N_3O_4$ requires 508.1295. Crystallographic description of **1**(R,S): Crystal dimensions (mm): 0.65 × 0.12 × 0.10. $C_{24}H_{18}F_5N_3O_4$, M_r = 507.42. T = 153(2) K. Monoclinic, space group $P_2(1)/c$; a = 7.2146(14) Å, b = 14.240(3) Å, c = 25.340(5) Å; β = 97.58(3)°; V = 2580.6(9) Å^3; Z = 4; D_{calc} = 1.455 g/cm^3; μ = 0.125 mm^{-1}; F(0 0 0) = 1168; Reflections collected/unique = 19,164/4508 [R(int) = 0.0655]; refinement method = full-matrix least-squares on F^2; final R indices [$I > \sigma 2(I)$] R_1 = 0.0679, wR_2 = 0.1698, R indices (all data) R_1 = 0.0892, wR_2 = 0.1922; goodness-of-fit on F^2 = 1.096; CCDC 679117.
10. Preparation of **2**(*R*,*S*) and **3**(*R*,*S*): Cyclic dipeptide N^{α}-CF_3CH_2(L)PheGly[1] (1.002 g, 3.50 mmol) was dissolved in 10 mL of dry DMF. NaH (95%, 0.575 mg, 22.7 mmol) was wetted with 30 mL of dry DMF. The cyclic dipeptide N^{α}-CF_3CH_2(L)PheGly solution was transferred into the NaH suspension in DMF. The reaction mixture was heated at 70 °C for 16 h. The solvent was evaporated. The resulting residue was partitioned between ethyl acetate and H_2O. The organic layer was separated and the solvent was evaporated. After column chromatography with 10–40% acetone in hexanes as eluent, **2**(*R*,*S*) (0.408 g, 1.37 mmol, 39.1%) and **3**(*R*,*S*) (0.468 g, 1.62 mmol, 46.3%) were obtained.
11. Spectral data of **2**(*R*,*S*): ^{19}F NMR (282.78 MHz, acetone-d_6): δ −69.51 (3F, t). ^{1}H NMR (300.53 MHz, acetone-d_6): δ 3.13–3.41 (2H, dd), 3.85–3.99 (1H, m), 4.50–4.53 (1H, m), 4.53 (1H, s), 4.83–4.98 (1H, m), 4.96 (1H, s), 7.05–7.26 (5H, m). Crystallographic description of **2**(*R*,*S*): Crystal dimensions (mm): 0.31 × 0.19 × 0.17. $C_{14}H_{13}F_3N_2O_2$, M_r = 298.26. T = 153(2) K. Orthorhombic, space group $P_2(1)2(1)2(1)$; a = 8.0516(16) Å, b = 14.837(3) Å, c = 23.102(5) Å; V = 2759.9(10) Å^3; Z = 8; D_{calc} = 1.436 g/cm^3; μ = 0.124 mm^{-1}; F(0 0 0) = 1232; Reflections collected/unique = 19,833/4892 [R(int) = 0.0496]; refinement method = full-matrix least-squares on F^2; final R indices [$I > \sigma 2(I)$] R_1 = 0.0477, wR_2 = 0.1185, R indices (all data) R_1 = 0.0557, wR_2 = 0.1261; goodness-of-fit on F^2 = 1.103; CCDC 679115.
12. Spectral data of **3**(*R*,*S*): ^{19}F NMR (282.78 MHz, acetone-d_6): δ −110.4 (1F, s). ^{1}H NMR (300.53 MHz, acetone-d_6): δ 3.05–3.29 (2H, dd), 4.39–4.74 (2H, dd), 4.44–4.87 (2H, d), 6.62 (1H, s), 6.99–7.26 (5H, m). Crystallographic description of **3**(*R*,*S*): Crystal dimensions (mm): 0.48 × 0.24 × 0.12. $C_{15}H_{13}FN_2O_3$, M_r = 288.27. T = 153(2) K. Triclinic, space group $P\bar{1}$; a = 10.599(2) Å, b = 11.296(2) Å, c = 18.369(4) Å; α = 100.47(3)°, β = 96.53(3)°, γ = 108.27(3)°; V = 2019.1(7) Å^3; Z = 6; D_{calc} = 1.422 g/cm^3; μ = 0.110 mm^{-1}; F(0 0 0) = 900; Reflections collected/unique = 13,994/7006 [R(int) = 0.0415]; refinement method = full-matrix least-squares on F^2; final R indices [$I > \sigma 2(I)$] R_1 = 0.0749, wR_2 = 0.1903, R indices (all data) R_1 = 0.1017, wR_2 = 0.2204; goodness-of-fit on F^2 = 1.094; CCDC 679116.
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