

Reactivity of 2-substituted hydrazinecarbothioamides towards tetracyanoethylene and convenient synthesis of (5-amino-2-diazenylthiazolylmethylene)malononitrile derivatives

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DOI: <https://doi.org/10.24820/ark.5550190.p009.872>

Abstract

2-{Amino-[5-amino-2-(substituted diazenyl)thiazol-4-yl]methylene}malononitriles were synthesized from the reaction of 2-substituted hydrazinecarbothioamides with tetracyanoethylene (TCNE) to give tetracyanoethane adduct, followed by heterocyclization afforded the target compounds. The structure of (*E*)-2-{amino-[5-amino-2-(phenyldiazenyl)thiazol-4-yl]methylene}malononitrile was supported by single crystal X-ray crystallography.

Keywords: Malononitrile, thiazoles, thiosemicarbazides, tetracyanoethylene, X-ray crystallography

Introduction

Recently, thiazole derivatives have attracted a great deal of interest due to their low toxicity and broad biological activity.¹⁻⁵ For example, naturally occurring and synthetic thiazoles find applications as antibiotics and anti-inflammatories,⁴⁻⁸ while selected aminothiazoles act as inhibitors of human cancer and Alzheimer`s disease.⁹⁻¹¹

The syntheses of thiazoles and 2-aminothiazoles have been studied extensively,^{12,13} however, the preparation of 5-aminothiazoles has not been so widely reported. Despite this, 5-aminothiazoles have received attention in a range of applications from antibiotics¹⁴ to photosensitizers.¹⁵

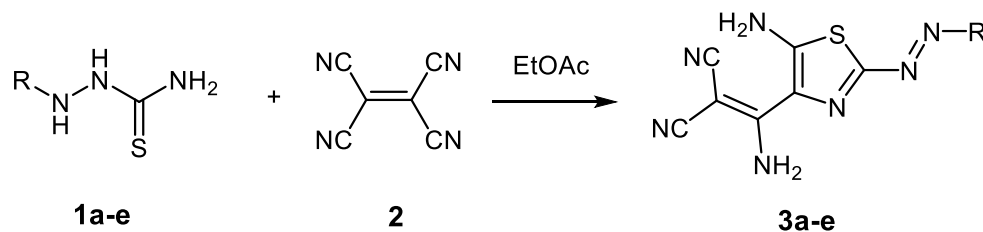
A convenient route to 5-amino-4-phenylthiazoles has been developed from *N*-acylated-glycinamides and Lawesson's reagent *via* trifluoroacetamides.¹² A flexible route to 5-amino-thiazoles has been developed based on cyclization of diamide adducts, prepared using the Ugi reaction,¹⁶⁻¹⁸ in presence of Lawesson's reagent.¹⁹ 5-Amino-3-(substituted benzylidenamino)-2-phenylimino-2,3-dihydrothiazole-4-carbonitrile is one of the products which have been isolated from the reaction of aldehyde thiosemicarbazones with tetracyanoethylene (TCNE).²⁰

Mesoionic 1,2,4-triazolium-3-thiolate derivatives were synthesized from the reaction of *N*-substituted 2-phenylhydrazinecarbothioamides with TCNE.²¹

Herein, we report our investigation on the reaction of 2-substituted hydrazinecarbothioamides **1a-e** with TCNE **2** (Fig. 1) and compared with the products isolated from the reaction of *N*-substituted 2-phenylhydrazinecarbothioamides with TCNE **2**.

Results and Discussion

Treatment of the hydrazinecarbothioamides **1a-e** with TCNE **2** (1.1 equiv) in dry ethyl acetate at room temperature resulted in a pink coloration of the reaction solution which quickly turned reddish orange. Tentatively, the color change observed may be owed to the formation of unstable charge-transfer (CT) complexes. The mixture was stirred and then left to stand for 24 hours at room temperature, resulting in the formation of single products **3a-e** in 81-88% yields (Scheme 1).



R = **a**: Ph; **b**: *p*-TolSO₂; **c**: Bn; **d**: CH₂=CH-CH₂ **e**: *m*-ClC₆H₄

1,3	R	Yields 3a-e , (%)
a	Ph	88
b	<i>p</i> -TolSO ₂	84
c	Bn	83
d	CH ₂ =CH-CH ₂	81
e	<i>m</i> -Cl-C ₆ H ₄	86

Scheme 1. Reactions of 2-substituted hydrazinecarbothioamides **1a-e** with TCNE **2**.

The gross formula C₁₃H₉N₇S represents a product from one molecule of **1a** and one molecule of TCNE **2** without elimination of any atoms. Two NH₂ groups are present in ¹H NMR (exchangeable with D₂O) as broad signals, the downfield at 10.22 ppm due to NH₂ attached to

vinyl group in **3a**, the other NH₂ resonate at 7.94 because of NH₂ attached to thiazole C5. The aromatic protons observed at 7.83-7.10 ppm. In its ¹³C NMR spectrum, thiazole C2, C4 and C5 resonate at 161.2, 150.4 and 152.6, respectively. In the (aminomethylene)malononitrile fragment, of **3a**, the dicyanovinyl carbons C2 and C1 resonated at 164.4 and 61.6 ppm, respectively, and were in accord with the observed trends in the δ values for C-atoms in push-pull alkenes.^{22,23} Further peaks at 115.6 (CN), besides the aromatic carbons support the assigned structure.

Absorption bands around 3373-3320 cm⁻¹ relating to NH₂ groups appeared in IR spectra of **3a-d**. The IR spectra of **3a-e** showed two sharp absorption bands at 2220-2210 cm⁻¹ (CN) and 1623-1612 cm⁻¹ that assigned to C=N vibration. The absence of C=S signal in IR and ¹³C NMR, also support the structures **3a-e**. Moreover, the structure of (*E*)-2-{amino-[5-amino-2-(phenyldiazenyl)thiazol-4-yl]methylene}malononitrile **3a** has been strongly supported by a single crystal X-ray structure analysis (Figure 1 and Tables S1-S7 in the supplementary data). The asymmetric unit of (*E*)-2-{amino-[5-amino-2-(phenyldiazenyl)thiazol-4-yl]methylene}malononitrile **3a** (C₁₃H₉N₇S), confirms two independent molecules whose conformations differ primarily in the orientations of phenyl and substituted vinyl groups with respect to the thiazole ring. The X-ray structure analysis confirms a *transoid* geometry of thiazole and substituted groups with respect to the N=N double bond.

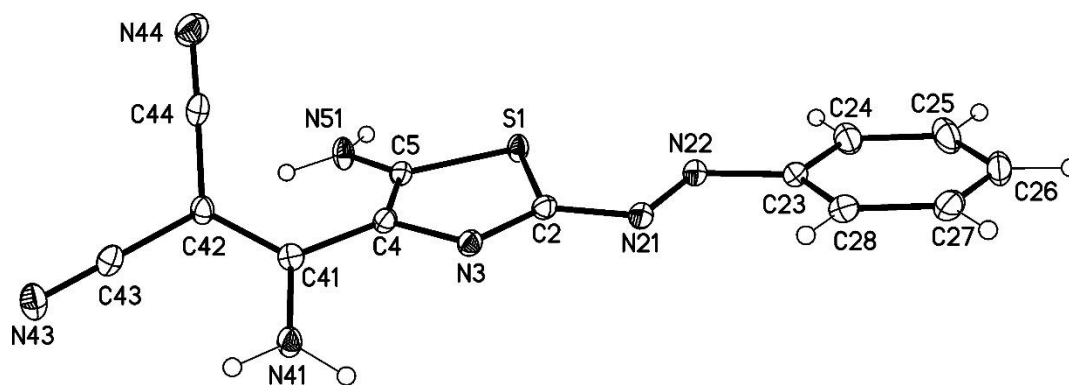
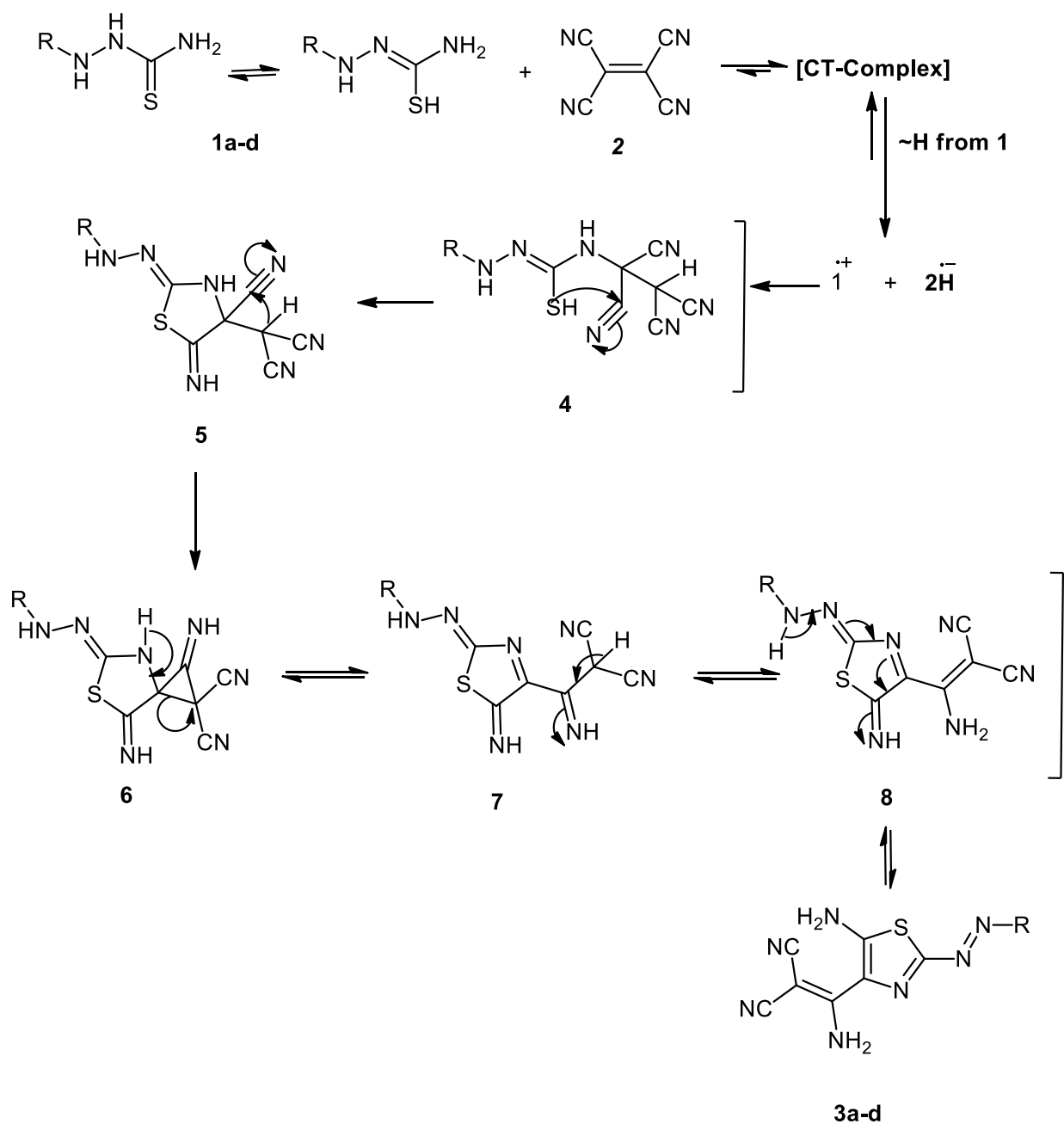


Figure 1. Molecular structure of **3a** in the crystal (TIF file). The crystallographic numbering does not reflect the systematic IUPAC numbering.

All bond lengths and angles in compound **3a** are normal. The thiazole ring is planar; mean deviation from the S1/C2/N3/C4/C5 plane 0.019 Å. The amino group and the planar phenyldiazenyl substituent are coplanar to the thiazole moiety, while the planar aminomethylenemalononitrile is twisted by 43° to the thiazole plane.

A rationale for the formation of compounds **3a-d** given in Scheme 2. Nucleophilic attack from the terminal NH₂ of **1a-d** on the C=C double bond of **2** to give the tetracyanoethane derivatives **4**; charge-transfer complexes may, but do not necessarily have to,²⁴ play an intermediate role. Intramolecular nucleophilic attack of SH of **4** on the C≡N triple bond and cyclization to give the intermediate **5** followed by the formation of bicyclic **6** that can open due to the proton transfer

from thiazole ring. Compound **6** can then rearrange to form **7** and **8** and finally the highly stable [amino-(5-amino-2-substituted diazenylthiazolyl)methylene]malono-nitriles **3a-e**.



Scheme 2: Mechanistic rationale for the formation of compounds **3a-e**.

Conclusions

In conclusion, novel (diazenylthiazolyl)methylene]malononitriles have been synthesized from the nucleophilic addition reactions of 2-substituted hydrazinecarbothioamides on TCNE. The products were synthesized from readily accessible starting materials using a simple experimental procedure.

Experimental Section

General. Gallenkamp melting point apparatus was used for determining the melting points; the results are uncorrected. The IR spectra (KBr discs technique) were recorded on Alpha, Bruker FT-IR and Shimadzu 408 instruments. The $^1\text{H-NMR}$ (400.13 MHz) and $^{13}\text{C-NMR}$ (100.6 MHz) spectra were determined on a Bruker AM 400 spectrometer; s = singlet, m = multiplet, b = broad. The ^{13}C NMR signals were assigned based on DEPT 135/90 spectra. Chemical shifts are expressed as δ in parts per million (ppm). The mass spectra (70 eV, electron impact mode) were recorded on a Finnigan MAT 312 instrument. The elemental analyses for C, H, N and S were carried out at the Microanalytical Centre, Cairo University, Egypt using an Elmyer 306. Preparative layer chromatography (PLC) used air-dried 1.0 mm thick layers of slurry-applied silica gel (Merck Pf₂₅₄) on glass plates 48 × 20 cm using the solvents listed.

Starting materials

The starting materials **1a-e** were prepared following published methods: **1a**,²⁵ **1b**,²⁶ **1c**,²⁷ **1d**,²⁸ and **1e**.²⁹ Tetracyanoethylene (TCNE, **2**) was bought from Fluka (USA), recrystallized from chlorobenzene and sublimed before used. Ethyl acetate and toluene were purified according to Vogel³⁰ and Organikum,³¹ dried and distilled. Acetonitrile (Merck) was used without further purification.

Reaction of 2-substituted hydrazinecarbothioamides **1a-e** with tetracyanoethylene (**2**).

General procedure. A solution of TCNE **2** (141 mg, 1.1 mmol) in dry EtOAc (10 mL), was added dropwise to a solution of **1a-e** (1.0 mmol) in dry EtOAc (15 mL), which causes a spontaneous change of color from yellow to pink and finally to reddish orange. The mixture was stirred for 2 h, then left to stand for 24 h at room temperature. A red-orange precipitate was formed, filtered and recrystallized from acetonitrile to give pure crystals **3a-e**. In case of the reaction between **1d** and TCNE **2**, the mixture of the reaction was subjected to PLC and using toluene/ethyl acetate (5:1) as eluent to give an intense red-orange zone from **3d**. The zone was separated by using acetone and recrystallized from acetonitrile.

(E)-2-{Amino-5-[amino-2-(phenyldiazenyl)thiazol-4-yl]methylene}malononitrile (3a**).** Red crystals (0.259 g, 88%), mp 231-233 °C (MeCN). IR: ν_{max} (KBr)/ cm^{-1} 3373-3342 (NH₂), 2215 (CN), 1620 (C=N), 1595 (Ar-C=C), 1571, 1455 (N=N) cm^{-1} . NMR: δ_{H} (400 MHz, DMSO-*d*₆) 7.10-7.12 (m, 1H, Ar-H), 7.60-7.62 (m, 2H, Ar-H), 7.80-7.83 (m, 2H, Ar-H), 7.95 (br, s, 2H, NH₂)

attached to thiazole), 10.22 (br, s, 2H, NH₂). δ_c (100 MHz, DMSO-*d*₆) 61.6 (C-C≡N), 115.6 (CN), 124.1, 128.6, 129.7 (Ar-CH), 133.0 (Ar-C), 150.5 (thiazole-C4), 152.6 (thiazole-C5), 161.2 (thiazole-C2), 164.4 (=C-NH₂). *m/z* (%): 295 (M⁺, 76), 268 (14), 190 (16), 105 (37), 77 (100). Anal. Calcd for C₁₃H₉N₇S (295.32) C, 52.87; H, 3.07; N, 33.20; S, 10.86. Found: C, 53.02; H, 2.94; N, 33.33; S, 10.71%.

(E)-2-{Amino-5-[amino-2-(4-toluenesulfonyldiazenyl)thiazol-4-yl]methylene}malononitrile (3b). Red crystals (0.313 g, 84%), mp 255-257 °C (MeCN). IR: ν_{\max} (KBr)/cm⁻¹ 3360-3320 (NH₂), 2210 (CN), 1617 (C=N), 1580 (Ar-C=C), 1565, 1446 (N=N) cm⁻¹. δ_H (400 MHz, DMSO-*d*₆) 2.42 (s, 3H, CH₃), 7.52-7.55 (m, 2H, Ar-H) 7.72-7.75 (m, 2H, Ar-H), 7.98 (br, s, 2H, NH₂ attached to thiazole), 10.31 (br, s, 2H, NH₂). δ_c (100 MHz, DMSO-*d*₆) 21.2 (CH₃), 61.4 (C-C≡N), 115.8 (CN), 125.2, 129.5 (Ar-CH), 135.7, 140.1 (Ar-C), 149.7 (thiazole-C4), 152.6 (thiazole-C5), 161.1 (thiazole-C2), 164.2 (=C-NH₂). *m/z* (%): 373 (M⁺, 12), 346 (18), 281 (100), 191 (19), 156 (16), 91 (46). Anal. Calcd for C₁₄H₁₁N₇O₂S₂ (373.41) C, 45.03; H, 2.97; N, 26.26; S, 17.17. Found: C, 44.89; H, 3.06; N, 26.12; S, 17.33%.

(E)-2-{Amino-[5-amino-2-(benzylidiazanyl)thiazol-4-yl]methylene}malononitrile (3c). Red-orange crystals (0.256 g, 83%), mp 242-244 °C (MeCN). IR: ν_{\max} (KBr)/cm⁻¹ 3366-3346 (NH₂), 2212 (CN), 1612 (C=N), 1589 (Ar-C=C), 1561, 1440 (N=N) cm⁻¹. δ_H (400 MHz, DMSO-*d*₆) 4.66 (s, 2H, CH₂Ph), 7.04-7.08 (m, 1H, Ar-H), 7.54-7.58 (m, 2H, Ar-H), 7.71-7.76 (m, 2H, Ar-H), 7.98 (br, s, 2H, NH₂ attached to thiazole), 10.29 (br, s, 2H, NH₂). δ_c (100 MHz, DMSO-*d*₆) 52.1 (CH₂Ph), 61.6 (C-C≡N), 116.0 (CN), 124.3, 128.5, 129.1 (Ar-CH), 133.6 (Ar-C), 149.7 (thiazole-C4), 152.5 (thiazole-C5), 161.2 (thiazole-C2), 164.4 (=C-NH₂). *m/z* (%) 309 (M⁺, 51), 282 (26), 204 (23), 91 (100). Anal. Calcd for C₁₄H₁₁N₇S (309.35) C, 54.36; H, 3.58; N, 31.69; S, 10.37. Found: C, 54.22; H, 3.66; N, 31.81; S, 10.23%.

(E)-2-[[2-(Allyldiazanyl)-5-aminothiazol-4-yl](amino)methylene]malononitrile (3d). Red-orange crystals (0.209 g, 81%), mp 167-169 °C (MeCN). ν_{\max} (KBr)/cm⁻¹ 3358-3326 (NH₂), 2210 (CN), 1615 (C=N), 1558, 1438 (N=N) cm⁻¹. δ_H (DMSO-*d*₆) 4.05-4.08 (m, 2H, allyl-CH₂N), 5.11-5.13 (m, 2H, allyl-CH₂=) 5.91-5.94 (m, 1H, allyl-CH=), 7.94 (br, s, 2H, NH₂ attached to thiazole), 10.16 (br, s, 2H, NH₂). δ_c (DMSO-*d*₆) 49.3 (allyl-CH₂N), 60.9 (C-C≡N), 115.0 (CN), 116.2 (allyl-CH₂=), 135.4 (allyl-CH=), 149.8 (thiazole-C4), 152.6 (thiazole-C5), 161.9 (thiazole-C2), 164.0 (=C-NH₂). *m/z* (%): 259 (M⁺, 21), 232 (26), 154 (46), 69 (37), 41 (100). Anal. Calcd for C₁₀H₉N₇S (259.29) C, 46.32; H, 3.50; N, 37.81; S, 12.37. Found: C, 46.45; H, 3.57; N, 37.93; S, 12.40%.

(E)-2-(Amino{5-amino-2-[(3-chlorophenyl)diazanyl]thiazol-4-yl}methylene)malononitrile (3e). Red-orange crystals (0.282 g, 86%), mp 248-250 °C (MeCN). IR: ν_{\max} (KBr)/cm⁻¹ 3365-3338 (NH₂), 2220 (CN), 1623 (C=N), 1583 (Ar-C=C), 1569, 1450 (N=N) cm⁻¹. NMR: δ_H (400 MHz, DMSO-*d*₆) 7.55-7.59 (m, 1H, Ar-H), 7.63-7.66 (m, 1H, Ar-H), 7.69-7.80 (m, 2H, Ar-H), 8.01 (br, s, 2H, NH₂ attached to thiazole), 10.28 (br, s, 2H, NH₂). δ_c (100 MHz, DMSO-*d*₆) 61.6 (C-C≡N), 115.8 (CN), 125.2, 126.3, 129.6, 130.1 (Ar-CH), 135.1, 141.2 (Ar-C), 149.7 (thiazole-C4), 153.1 (thiazole-C5), 161.2 (thiazole-C2), 164.5 (=C-NH₂). *m/z* (%): 329 (M⁺, 36), 218 (28), 190 (61), 139 (43), 111 (100). Anal. Calcd for C₁₃H₈ClN₇S (329.77) C, 47.35; H, 2.45; N, 29.73; S, 9.72. Found: C, 47.42; H, 2.36; N, 29.61; S, 9.83%.

Single crystal X-ray structure determination of **3a**

Single crystals were obtained by recrystallization from acetonitrile. The single crystal X-ray diffraction study was carried out on a Bruker D8 Venture diffractometer with Photon100 detector at 123 K using CuK α radiation ($\lambda = 1.54178 \text{ \AA}$) **3a**. Direct Methods (SHELXS-97)³² were used for structure solution and refinement was carried out using SHELXL-2014³³ (full-matrix least-squares on F^2). Hydrogen atoms were localized by difference electron density determination and refined using a riding model (H (N) free). A semi-empirical absorption correction was applied.

Compound **3a**: C₁₃H₉N₇S, M = 295.32 g mol⁻¹, red plates, crystal size 0.12 × 0.08 × 0.02 mm, triclinic space group, P-1 (no. 2), a = 7.3780 (4) Å, b = 7.9678 (5) Å, c = 11.9389 (7) Å, $\alpha = 99.249 (2)^\circ$, $\beta = 104.589 (2)^\circ$, $\gamma = 100.386 (2)^\circ$, V = 652.23 (7) Å³, Z = 2, D_{calcd} = 1.504 Mg m³, F(000) = 304, $\mu = 2.256 \text{ mm}^{-1}$, T = 123 K, 11384 measured reflections ($2\theta_{\text{max}} = 144^\circ$), 2540 independent reflections [$R_{\text{int}} = 0.030$], 202 parameters, 4 restraints, R1 [for 2405 reflections with $I > 2\sigma(I)$] = 0.028, wR² (for all data) = 0.068, S = 1.06, largest diff. peak and hole = 0.266 eÅ⁻³/- 0.245 eÅ⁻³.

Crystallographic data (excluding structure factors) for structure reported in this work have been deposited with Cambridge Crystallographic Data center as supplementary publication no 1048447 (**3a**) Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223) 336 033; e-mail: deposit@ccdc.cam.ac.uk).

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