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COMMUNICATION

En route towards α-benzotriazoyl nitroso derivatives†

Jean-Christophe M. Monbaliu,[ab] Lucas K. Beagle,[a] Judit Kovacs,[a] Matthias Zeller,[c] Christian V. Stevens[b] and Alan R. Katritzky*[ad]

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A new class of geminally-substituted nitroso compounds, *i.e.* α-benzotriazoyl nitroso derivatives, is presented. These compounds display a rather different behavior than other related nitroso compounds bearing a geminal electron-withdrawing group. An unexpected and spontaneous oxidation to the nitro analog is observed in solution.

1 Introduction

Nitroso compounds have emerged during the last decades as prominent reagents for the hydroxylation and amination of a wide variety of substrates, leading to useful 1,2-oxazines, nitrones and other aminohydroxylated building blocks.[1a–e] Numerous examples of nitroso Diels–Alder cycloaddition (nDA),[2a–c] nitroso-ene[3a–c] and nitroso-aldol[4a–b] reactions are already known. Recently, Srivastava and coworkers reported a promising gold-catalyzed annulation of nitroso arenes and alkynes.[5] The nDA has been one of the most successfully incorporated nitroso reactions as the key step in the total synthesis of a broad range of biologically active molecules.[1a,6a–m] A wide variety of nitroso reagents have emerged, ranging from the very reactive (transient) acyl nitroso compounds to the rather stable nitroso arenes.[7a,b] Among these, geminally functionalized nitroso compounds (α-EWG-NO) are of particular interest: they have offered synthetic advantages in affording free 1,2-oxazines upon solvolysis of the initial Diels–Alder cycloadduct,[7b] and also found biological applications for the release of nitrogen oxide (NO) and nitroxyl (HNO).[8a–e] α-Chloro-[9] and α-acetoxy nitroso[10a–c] derivatives are amongst the most commonly used α-EWG-NO dienophiles, although α-cyanonitroso dienophiles have been also reported.[11]

Their *in vitro* and *in vivo* NO/HNO-related vasodilating activities were spotlighted in 2000 by Gasco and coworkers.[8e] A few years later, a seminal study by King[8d] led to the development of a series of promising α-acetoxy nitroso compounds which slowly release HNO upon hydrolysis under physiological conditions and have been proven to be vasorelaxant.[8a,b] In 2009, Toone *et al.* demonstrated that α-cyano nitroso compounds behave as NO donors.[8c]

This context has prompted us to assess α-benzotriazoyl nitroso derivatives as a new class of reagents. 1*H*-Benzotriazole has been shown to be an extremely versatile synthetic auxiliary in organic chemistry.[12a–d] We now document the synthesis, properties and reactivity of a new class of α-EWG nitroso compounds. X-ray, kinetic and computational studies rationalise the phenomena observed.

2 Results and discussion

2.1 Preparation of α-benzotriazoyl nitroso derivatives

Our first attempt to synthesize α-benzotriazoyl nitroso derivatives from their corresponding oximes **1a–c** (Scheme 1) utilized 1-chloro-1*H*-benzo[*d*][1,2,3]triazole (1-CBT, **2**) as an oxidizer.[13a–d]

1-CBT (**2**) was prepared on a large scale according to a reported procedure[14] and obtained in high purity after recrystallization.[15] 1-CBT (**2**) displays global[16a–h] and local[17] electronic properties of interest for an oxidizer (Fig. 1): a moderate electrophilicity (ω = 1.7 eV), in contrast with other commonly used oxidizers which often lead to the overoxidation of oximes to nitro,[18a,b] and a strongly electropositive chlorine atom (f^{+}_{Cl} = 0.64) combined with the potential release of the nucleophilic benzotriazolate anion *in situ*.

Despite these very promising features, the reaction of several oximes (**1** in Scheme 1) in the presence of 1-CBT led exclusively to the formation of the corresponding α-chloro nitroso derivatives **3a–c** in quantitative yields (Scheme 1). The incorporation of various additives (1*H*-benzo[*d*][1,2,3]triazole, sodium benzotriazolate) in the protocol did not affect the reaction. Computed heterolytic and homolytic bond dissociation enthalpies of 1-CBT revealed that the likelihood of a radical mechanism is much higher (ΔH^{homo} = 48.4, 44.8 and 44.7 kcal mol^{-1} in gas phase, THF and DCM, respectively) than the expected heterolytic mechanism (ΔH^{hetero} = 318.9, 206.8, 203.7 kcal mol^{-1} in gas phase, THF and DCM, respectively), in agreement with our experimental observations (see Supporting Information† for details).

Recent work by King[8d] and by Kouklovsky and Vincent[10b] suggested $Pb^{IV}(OAc)_4$ and iodobenzene diacetate-based reagents, and we obtained the best results from a preformed mixture of lead

[a]*Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, FL 32611-7200, USA. E-mail: katritzky@chem.ufl.edu*
[b]*Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, B-9000 Ghent, Belgium*
[c]*Department of Chemistry, Youngstown State University, Youngstown, OH-44555, USA*
[d]*Chemistry Department, King Abdulaziz University, Jeddah, 21589 Saudi Arabia*

† Electronic Supplementary Information (ESI) available: Detailed computational procedures, cartesian coordinates for the isolated transitions states, kinetic data, ^{1}H and ^{13}C NMR for compounds **4c** and **6** and thermogravimetric analysis of 1-CBT. CCDC 883509-883510. See DOI: 10.1039/c2ra21311g

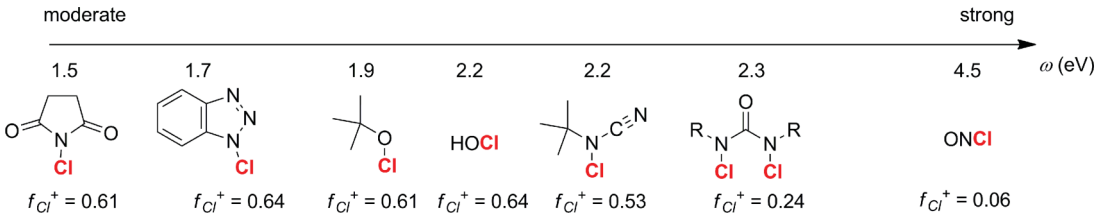


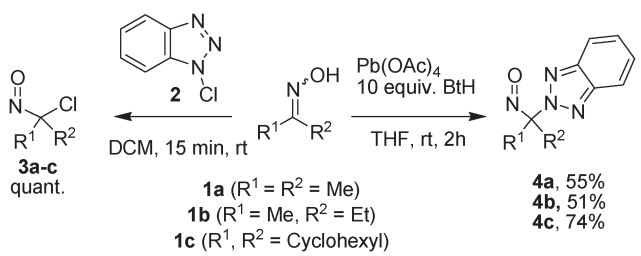
Fig. 1 Global and local electronic properties for a selected series of nitrosation reagents (see refs 18*a*,*b* and 19*a*–*d* for experimental details). The compounds are scaled according to their global electrophilicity (ω) and local Fukui functions f^+_{Cl} are indicated for the chlorine atom. The global electrophilicity was computed according to the procedure introduced by Domingo[16*a*–*h*] and the Fukui functions were obtained using the procedure of Contreras.[17]

tetraacetate and benzotriazole (10 equiv.). Alkyl oximes derived from acetone (**1a**), 2-butanone (**1b**), and cyclohexanone (**1c**) led to their corresponding α-benzotriazoyl nitroso derivatives **4a** (55%), **4b** (51%) and **4c** (74%) in dry THF at room temperature (Scheme 1).[20] In dry dichloromethane, the corresponding yields were considerably lower.

2.2 Properties of α-benzotriazoyl nitroso derivatives

The behavior of nitroso compounds **4a,b** differed from that of **4c**. Compounds **4a,b** formed white powders, but bright blue solutions, suggesting that the azodioxy dimer is the major form in the solid state but dissociates in solution into the monomeric nitroso derivative. This was confirmed by the observation of a signal at ~1290 cm^{-1} in the solid state IR spectra. Contrastingly, compound **4c** was isolated as a monomeric nitroso derivative. The shelf-life of compound **4c** was over 4 months at room temperature, in deep contrast with the short shelf-life of its chloro- and acetoxy-analogs. The chloro-analog **3c** decomposed after 3 days at −10 °C.

Compound **4c** was submitted for single crystal X-ray diffraction, resulting in interesting information about the solid state and confirming the monomeric nitroso structure (see Supporting Information†). The benzotriazoyl moiety appeared to be exclusively bonded at the quaternary carbon *via* the N^2 position. From the collected X-ray data sets, a single *endo* conformer of compound **4c** was detected (with nitroso group in an equatorial position and *endo versus* the benzotriazoyl system). This specific conformation could result either from the emergence of favorable π-system interactions, electrostatic repulsion between the lone pair of the nitrogen and the aromatic benzotriazoyl system (*exo lone pair* effect),[21] or a combination of both phenomena. Computations at the B3LYP/6-31+G* level of theory showed that the conformer bearing the ^{2}Bt substituent in an axial position and the nitroso moiety in a relative equatorial *endo* position was indeed the most stable. This specific relative position allows for the antiperiplanar alignment of the NO nitrogen lone pair and the $\sigma^*_{C\text{-}Bt2}$ and therefore increased vicinal negative hyperconjugation.[22] A NBO[23] analysis confirmed this assumption and showed that the nitrogen N^2 lone pair on the benzotriazole substituent was similarly involved in a strong stabilizing negative hyperconjugation with the $\sigma^*_{C\text{-}NO}$, consequently weakening the corresponding σ bond.



Scheme 1 Reactivity of 1-CBT and preparation of α-benzotriazoyl nitroso derivatives.

2.3 Reactivity of α-benzotriazoyl nitroso derivatives

The computed global electrophilicity (ω) of α-benzotriazoyl nitroso compound **4c** allowed its ranking on the electrophilicity scale.[16*a*–*h*] Compound **4c** showed up in the same electrophilicity range (ω_{Bt} = 2.6 eV) as its chloro- and acetoxy-analogs (ω_{Cl} = 2.6 eV and ω_{AcO} = 2.9 eV), *i.e.* as a moderate electrophile. Interestingly, compound **4c** was inactive as a dienophile even after prolonged reaction time in the presence of an excess of 2,3-dimethylbutadiene or cyclopentadiene in various solvents (see Supporting Information†), while its chloro- and acetoxy-congeners have been known as dienophiles for decades.[7*b*,9,10*a*-*c*] This experimental observation contrasted with the rather similar computed activation barriers for the cycloaddition of model 2-nitrosopropane (**A**), benzotriazoyl- (**B**), chloro (**C**)- and acetoxy-derivatives (**D**) (Fig. 2). The cycloaddition step was computed for 2-nitrosopropane (**A**) in order to scout the impact of the leaving group on the cycloaddition step.

The activation barriers for the cycloaddition step (B3LYP/6-31+G*) were relatively independent of the nature of the leaving group (Fig. 2). To explain the observed lack of dienophile character for compound **4c**, two main hypotheses have risen: (*i*) a more pronounced impact of the nature of the leaving group on the subsequent steps (*i.e.* elimination and solvolysis) (*ii*) the existence of a

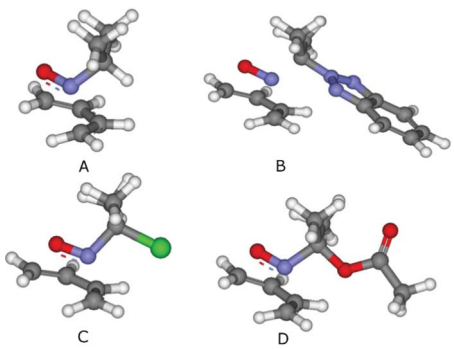
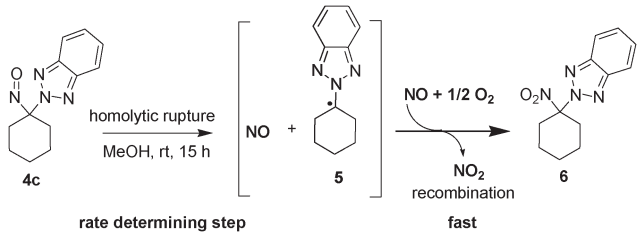


Fig. 2 Picture of the TSs associated with the cycloaddition of the selected model nitroso compounds onto butadiene. For each situation, 4 isomeric TSs have been isolated due to the relative *endo*/*exo* approach of the dienophile and the relative *syn*/*anti* orientation of the EWG group *vs.* N=O. The results presented are relative to the most stable TS (*endo*/*anti*; see details in the Supporting Information†). Activation free energies ($\Delta G^{\neq}$) are indicated in kcal mol^{-1}: A: 26.6; B 27.3; C 27.2; D: 26.5.



Scheme 2 Proposed mechanism for the formation of 2-(1-nitrocyclohexyl)-2*H*-benzo[*d*][1,2,3]triazole **6** from **4c**.

competitive reaction pathway for **4c** in solution. The first hypothesis was dismissed on the basis of the excellent abilities of benzotriazole to act as leaving group in a plethora of reactions.[12a–d] The second hypothesis materialized upon the observation of various side-products depending on the reaction conditions. When solutions of compound **4c** in various solvents were left in an open flask for 15 h, compound **4c** was quantitatively converted into 2-(1-nitrocyclohexyl)-2*H*-benzo[*d*][1,2,3]triazole **6** (Scheme 2), whereas in degassed and dry THF a complex mixture was observed after 15 h, likely arising from the spin-trapping of radicals by **4c**.[8c,24] Addition of TEMPO to a degassed solution of **4c** led to the progressive disappearance of the typical blue coloration of **4c** and formed a complex mixture of spin-trapped compounds.[8c,24]

The rationale for the mechanism depicted in Scheme 2 was built on the following observations and computations: (*i*) apparent first order k_{obs} = 3.1, 2.0, 1.8 and 1.4 × 10^{-5} s^{-1} were determined in methanol, acetonitrile–water, acetonitrile and dichloromethane, respectively (Fig. 3); (*ii*) the presence of a large excess of oxygen (bubbled through the solution) did not impact on the rate of disappearance; (*iii*) rather high one-electron redox potentials E° were computed and (*iv*) isodesmic heat (ΔH^{iso}) for radical exchange, radical stabilization energies (RSE)[25] as well as homolytic bond

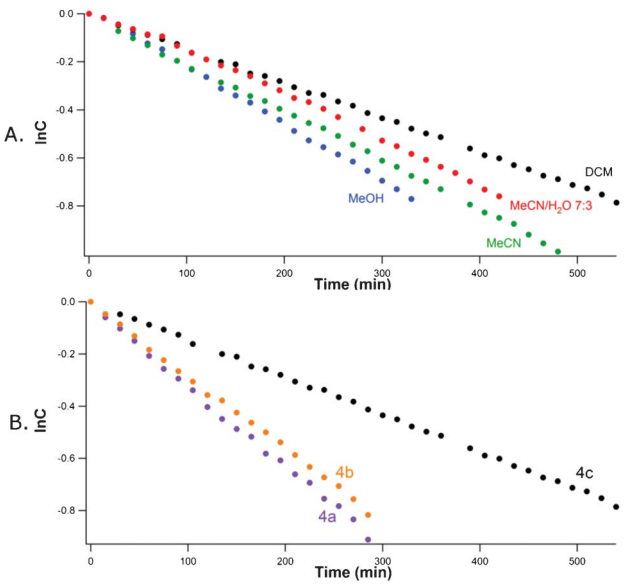
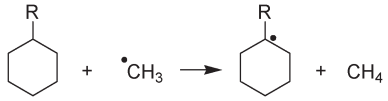


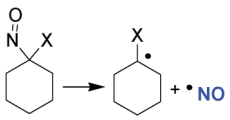
Fig. 3 (A.) Apparent (k_{obs}) first order disappearance of **4c** in different solvents (top) and of compounds **4a–c** in dichloromethane (bottom). (B.) The kinetics for the disappearance of compounds **4a–c** were determined by UV-spectrophotometry at 20 °C in different solvents by following the decrease of the typical nitroso signal (λ_{max} = 655.7 nm, 10 mg mL^{-1}).

Table 1 Isodesmic reactions for radical exchange on different cyclohexyl substrates and corresponding radical stabilization energy (RSE)



R	ΔH^{iso} (kcal mol^{-1})	RSE (kcal mol^{-1})
Me	−10.8	10.8
Cl	−10.2	10.2
Ph	−19.3	19.3
^{2}Bt	−30.9	30.9

Table 2 Homolytic bond dissociation energies (BDE) for compounds **4c**, **4d** and **3c**



X	BDE (kcal mol^{-1})
^{2}Bt (**4c**)	22.4
CN (**4d**)	19.8
Cl (**3c**)	30.6

dissociation energies (BDE) for compounds **4c**, **4d** and **3c** were computed (Tables 1–2).

The kinetics display only moderate dependency on solvent polarity which suggested implication of radical species rather than charged intermediates. An additional set of experiments using different concentrations (5 and 20 mg mL^{-1}) for compound **4c** in acetonitrile gave different half times ($t_{1/2}$ = 266.6 and 495.1 min, respectively). This observation is consistent with the formation of an *inactive reservoir* of nitroso compound **4c** as its azodioxy dimer at higher concentration. The second observation, *i.e.* the apparent lack of impact of an excess of oxygen in the reaction mixture, reinforced the mechanism proposed in Scheme 2. As per Fig. 2, the steric hindrance of the backbone on $^{\alpha}$C has a profound impact on the reactivity ($t_{1/2}$ = 223.6 (**4a**), 247.6 (**4b**) and 495.1(**4c**) min).

The one-electron redox potential E° was computed in methanol using standard procedures (see free energy cycles in the Supporting Information†).[26a,b] E° (MeOH) = 5.5, 6.4 and 6.2 V for **4c**, **4d** and **3c**, respectively (E° = 6.5 V for the reference MeNO) indicated that these compounds are quite resistant to oxidation and require strong oxidizers, in agreement with previously reported data.[27a–c]

RSE emphasized that the ^{2}Bt substituent stabilizes a radical much better than a phenyl does (Table 1). Further proof was obtained by computing homolytic bond dissociation energies (BDE) for the release of nitric oxide from compounds **4c**, **4d** and **3c** (see Supporting Information† for heterolytic bond dissociation energies). These revealed that the homolytic bond rupture for the benzotriazoyl compound was very close to the value obtained for the reference **4d** (Table 2),[8c] emphasizing its propensity to release the radical intermediate **5** (Scheme 2). The release of NO was not detected by GC-MS; subsequent rapid oxidation of the side product NO by atmospheric oxygen led to nitrogen dioxide,[28a] which very likely underwent recombination with the stabilized radical **5**.[28a–d] Compound **6**, the structure of which has been unambiguously

determined by X-ray diffraction, was exclusively formed under aerobic conditions.[29]

3 Conclusion

In this communication, we have documented the synthesis, properties and reactivity of a new class of reagents, namely α-benzotriazoyl nitroso compounds. α-Benzotriazoyl nitroso compounds were conveniently obtained *via* the oxidation of the corresponding oximes in the presence of lead tetraacetate and a large excess of benzotriazole. The benzotriazole is anchored to the nitroso-substrate exclusively at the ^{2}N position. Despite comparable activation barriers, α-benzotriazoyl nitroso compounds were not reactive towards dienes, in contrast with their α-chloro and α-acetoxy analogs. An unexpected oxidation – not observed for other α-EWG analogs – was found to occur in solution leading to the exclusive formation of α-benzotriazoyl nitro compounds. The mechanism most likely involves a rate-determining homolytic cleavage of the parent nitroso, releasing NO which is readily oxidized in solution, followed by subsequent recombination to yield the nitro analog.

Acknowledgements

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15 Caution! 1-Chloro-1*H*-benzo[*d*][1,2,3]triazole (1-CBT) is a shock- and heat-sensitive material. There is little to no specific hazard associated with the synthesis of 1-CBT as reported in ref. 14. The recrystallization in boiling hexane–dichloromethane must be carried out on a small scale (<1 g) behind a blast shield. The white crystals obtained after recrystallization (mp 108.0–109.0 °C) are extremely shock sensitive. Thermogravimetric (TGA) analysis showed that 1-CBT starts decomposing at 90 °C; at 113.5 °C, 50.3% wt of the sample was lost. The heat of combustion was measured: $\Delta U^{c} = 0.82$ Mcal mol^{-1}.

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20 **Procedure for the synthesis of 2-(1-nitrosocyclohexyl)-2*H*-benzo[*d*][1,2,3]triazole 4c.** A solution of lead(IV) tetraacetate (4.43 g, 10.0 mmol) and 1*H*-benzotriazole (11.81 g, 100.0 mmol) in dry THF (100 mL) was stirred for 15 min at 0 °C. The resulting homogeneous solution was treated dropwise with a solution of cyclohexanone oxime (1.13 g, 10.0 mmol) in dry THF (10 mL) over 15 min at 0 °C. After 2 h, the solvent was removed under reduced pressure and the brown residue was triturated several times with hexanes (5 × 50 mL) containing 10% of ethyl acetate. The combined organic fractions were evaporated under reduced pressure and the greenish

oily residue was purified by column chromatography over silica gel (hexanes–ethyl acetate 10 : 1) to give 2-(1-nitrosocyclohexyl)-2*H*-benzo[*d*][1,2,3]triazole as a blue solid. Yield: 74% (1.70 g, 7.4 mmol), blue microcrystals. m.p. 125.0–127.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34–1.51 (m, 2H), 1.55–1.67 (m, 1H), 1.67–1.80 (m, 1H), 1.94–2.06 (m, 2H), 2.65–2.86 (m, 4H), 7.36–7.45 (m, 2H), 7.84–7.93 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 24.6, 29.2, 118.7, 127.0, 128.1, 144.9 ppm. Elemental analysis calcd (%) for $C_{12}H_{14}N_4O_1$: C, 62.59; H, 6.13; N, 24.33; found: C, 62.20; H, 5.90; N, 24.41. Crystal data for compound **4c**: blue crystal (plates), dimensions 0.4 × 0.1 × 0.04 mm, crystal system monoclinic, space group $P2_1/c$, Z = 4, a = 11.7352(5), b = 8.5659(3), c = 12.1021(4) Å, β = 110.616(2)°, V = 1138.63(7) Å^3, ρ = 1.349 g cm^{-3}, T = 100(2) K, Θmax = 30.60°, radiation Mo-Kα, λ = 0.71073 Å, 0.3 ω-scans with CCD area detector, covering a whole sphere in reciprocal space, 14435 reflections measured, 3407 unique (R_{int} = 0.0218), 2873 observed ($I > 2\sigma(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS22 based on the Laue symmetry of the reciprocal space, m = 0.091 mm^{-1}, Tmin = 0.6840, Tmax = 0.7461, structure solved by direct methods and refined against $F2$ with a full-matrix least-squares algorithm using the SHELXL-97 software package, 164 parameters refined, hydrogenatoms were treated using appropriate riding models, goodness of fit = 1.069 for observed reflections, final residual values $R1(F)$ = 0.0376, w$R(F2)$ = 0.0976 for observed reflections. CCDC 883509†.

21 The *exo lone pair effect*, *i.e.* the preferential *endo* approach of nitrosodienophiles in Diels–Alder reactions, has been introduced by Houk *et al.* (see M. A. McCarrick, Y.-dong Wu and K. N. Houk, *J. Am. Chem. Soc.*, 1992, **114**, 1499–1500). The minimization of the electrostatic repulsions between the diene and the dienophile leads to a highly favored *endo* approach, releasing the nitrogen lone pair of the nitroso in the *exo* position.

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29 **Procedure for the synthesis of 2-(1-nitrocyclohexyl)-2*H*-benzo[*d*][1,2,3]triazole 6.** A solution of 2-(1-nitrosocyclohexyl)-2*H*-benzo[*d*][1,2,3]triazole **4c** (1.15 g, 5.0 mmol) in 50 mL dry methanol was stirred for 15 h in an open flask. The solvent was evaporated and the resulting white solid was recrystallized from a 10 : 1 hexanes–dichloromethane mixture. Yield: 92% (1.21 g, 4.9 mmol), white microcrystals. m.p. 143.0–145.0 °C. ^{1}H (300 MHz, $CDCl_3$): 1.30–1.72 (m, 4H), 1.86–1.99 (m, 2H), 2.72 (dt, J = 13.1, 13.1, 4.0 Hz, 1H), 3.44–3.44 (m, 2H), 7.41–7.49 (m, 2H), 7.86–7.95 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6, 24.0, 34.1, 105.1, 119.1, 128.1, 145.0 ppm. Crystal data for compound **6**: white crystal (rods), dimensions 0.55 × 0.29 × 0.26 mm, crystal system orthorhombic, space group $P2_12_12_1$, Z = 4, a = 5.9246(9), b = 11.7114(19), c = 16.898(3) Å, β = 90.00°, V = 1172.5(3) Å^3, ρ = 1.395 g cm^{-3}, T = 100(2) K, Θmax = 31.73°, radiation Mo-Kα, λ = 0.71073 Å, 0.3 ω-scans with CCD area detector, covering a whole sphere in reciprocal space, 8626 reflections measured, 2124 unique (R_{int} = 0.0554), 2045 observed ($I > 2\sigma(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS22 based on the Laue symmetry of the reciprocal space, m = 0.099 mm^{-1}, Tmin = 0.6747, Tmax = 0.7463, structure solved by direct methods and refined against $F2$ with a full-matrix least-squares algorithm using the SHELXL-97 software package, 163 parameters refined, hydrogen atoms were treated using appropriate riding models, goodness of fit = 1.071 for observed reflections, final residual values $R1(F)$ = 0.0346, w$R(F2)$ = 0.0888 for observed reflections. CCDC 883510†.