Accepted Manuscript

1,3-Dipolar cycloaddition between acetylenic dipolarophiles and sydnone-*N*-ylides as bis(1,3-dipoles)

Florin Albota, Drăghici Constantin, Mino R. Caira, Florea Dumitrascu

PII: S0040-4020(15)30121-6

DOI: 10.1016/j.tet.2015.10.021

Reference: TET 27193

To appear in: *Tetrahedron*

Received Date: 23 June 2015

Revised Date: 24 September 2015

Accepted Date: 6 October 2015

Please cite this article as: Albota F, Constantin D, Caira MR, Dumitrascu F, 1,3-Dipolar cycloaddition between acetylenic dipolarophiles and sydnone-*N*-ylides as bis(1,3-dipoles), *Tetrahedron* (2015), doi: 10.1016/j.tet.2015.10.021.

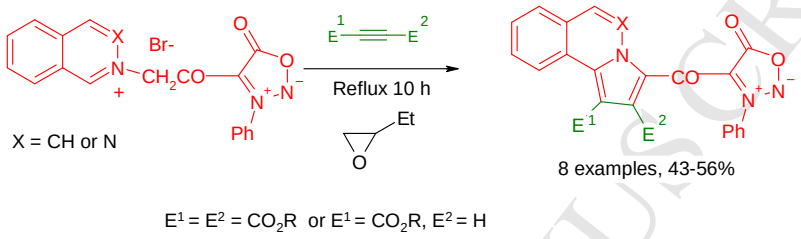
1,3-Dipolar cycloaddition between acetylenic dipolarophiles and sydnone-*N*-ylides as bis(1,3-dipoles)

Leave this area blank for abstract info.

Florin Albota[a], *Drăghici Constantin*[a], *Mino R. Caira*[b,*], *Florea Dumitrascu*[a,*]

[a] Centre of Organic Chemistry ''C. D. Nenitzescu'', Roumanian Academy, Spl Independent ei 202B, 060023 Bucharest, Romania

[b] Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa



$E^1 = E^2 = CO_2R$ or $E^1 = CO_2R$, $E^2 = H$

Tetrahedron
journal homepage: www.elsevier.com

1,3-Dipolar cycloaddition between acetylenic dipolarophiles and sydnone-*N*-ylides as bis(1,3-dipoles)

Florin Albota[a], Drăghici Constantin[a], Mino R. Caira[b,*], Florea Dumitrascu[a,*]
[a] Centre of Organic Chemistry ''C. D. Nenitzescu'', Roumanian Academy, Spl Independenței 202B, 060023 Bucharest, Romania
[b] Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Sydnone-*N*-ylides
bis(1,3-dipoles)
1,3-dipolar cycloaddition
pyrrolo[2,1-*a*]phthalazine
pyrrolo[2,1-*a*]isoquinoline

ABSTRACT

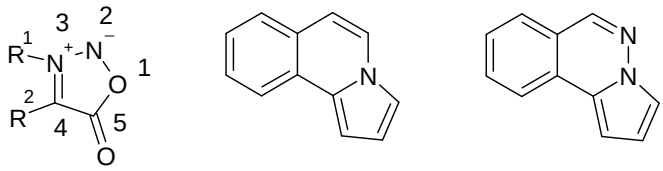
1,3-Dipolar cycloaddition reaction of sydnone-*N*-ylides, as model *bis*(1,3-dipoles), with acetylenic dipolarophiles in 1,2-epoxybutane under reflux gave exclusively pyrroloazines containing a sydnone moiety that resulted by preferred reaction of the *N*-ylide 1,3-dipole with the acetylenic dipolarophiles. The assembled sydnone-ylide hybrid structures were generated *in situ* from *N*-heteroaromatic bromides. The structure of the new compounds was assigned by IR and NMR spectroscopy and confirmed by X-ray analysis for a representative compound.

1. Introduction

Sydnones are mesoionic heterocyclic compounds with a 1,2,3-oxadiazole skeleton. They were discovered in 1935 by Earl and Mackney[1] and their mesoionic structure was assigned in 1949 by Baker and Ollis.[2] Sydnones present an array of biological properties such as antibacterial,[3,5] antifungal,[3,5] antimicrobial,[4-6] anticancer,[5,7] antiproliferative,[8] anti-HIV,[8] anti-inflammatory and analgesic activities.[9]

Sydnones (Figure 1) undergo two main chemical reactions, namely 1,3-dipolar cycloaddition to form pyrazoles and electrophilic substitution at C-4.[10] The hydrogen atom at position 4 of the sydnone ring can be substituted with a wide variety of electrophiles *via* e.g. chlorination,[11] bromination,[11] iodination,[11-13] and acylation.[14] The most important chemical reaction of sydnones is 1,3-dipolar cycloaddition with alkynes to give pyrazoles that have numerous applications as pharmaceuticals and agrochemicals.[15-21]

Also, the sydnones served as a key intermediate in the synthesis of the alkaloid withasomnine[22] and as starting material for obtaining other heterocyclic compounds.[19]



1 **2** **3**

Fig. 1. The structure of sydnone **1**, pyrrolo[2,1-*a*]isoquinoline **2** and pyrrolo[2,1-*a*]phthalazine **3**.

As a result of their interesting chemistry, biological and physicochemical properties, sydnones have already been the subject of various reviews.[10,23,24]

On the other hand, the pyrroloazines, pyrrolo[2,1-*a*]phthalazines and pyrrolo[2,1-*a*]isoquinolines have attracted more attention due to their biological[25-30] and optical[31,32] properties. Furthermore, pyrrolo[2,1-*a*]isoquinoline serves as the scaffold of important classes of alkaloids such as lamellarins, crispine, salsoline, erythrina and annosqualine.[33] The most versatile method of synthesis of pyrroloazines is the 1,3-dipolar cycloaddition reaction between heteroaromatic *N*-ylides and acetylenic dipolarophiles.[34-52]

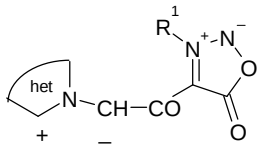
Herein we report the generation of sydnone-*N*-ylides as *bis*(1,3-dipoles) and their reactivity in the 1,3-dipolar cycloaddition reaction with acetylenic dipolarophiles.

a* e-mail: fdumitra@yahoo.com

b* Tel.: +27-21-650-3071; fax: +27-21-650-5195; e-mail: Mino.Caira@uct.ac.za

2. Results and discussion

Based on the capacity of a sydnone and a heteroaromatic *N*-ylide to act as 1,3-dipoles in 3+2 cycloaddition reaction, our intention was to assemble the sydnone and *N*-ylide 1,3-dipoles within the same molecule (Figure 2) and to investigate the reactivity of the resulting *bis*(1,3-dipole) towards acetylenic dipolarophiles.



4

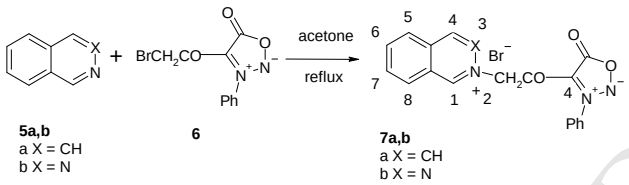
N-ylide 1,3-dipole sydnone 1,3-dipole

het = heteroaromatic *N*-heterocycle

Fig. 2. The structure of sydnone-*N*-ylides **4.**

2.1. Synthesis of azinium salts 7

The starting materials for the generation of sydnone-*N*-ylides **4** were the bromides **7a,b** which were synthesized in good yields by the quaternization reaction of isoquinoline and phthalazine **5a,b** with 4-bromoacetyl-3-phenylsydnone **6** (Scheme 1). The azinium bromides **7a,b** were subsequently used in the generation of sydnone-*N*-ylides **4**.



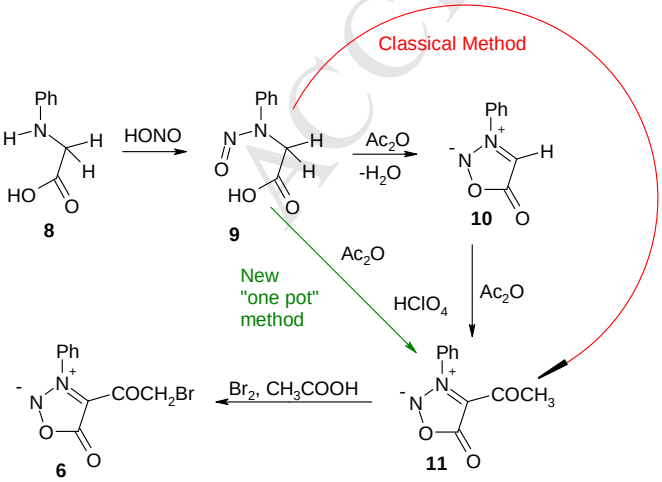
5a,b
a X = CH
b X = N

6

7a,b
a X = CH
b X = N

Scheme 1. Synthesis of bromides **7a,b**.

The 4-bromoacetyl-3-phenylsydnone **6** was synthesized using a method described in the literature[53] starting from the commercial product *N*-phenylglycine **8** (Scheme 2). In the process of synthesizing compound **6** we developed an improved method for the preparation of 4-acetyl-3-phenylsydnone **11** by performing in only one step the cyclization of the *N*-nitroso-*N*-phenylglycine **9** to 3-phenylsydnone **10** followed by its acetylation.



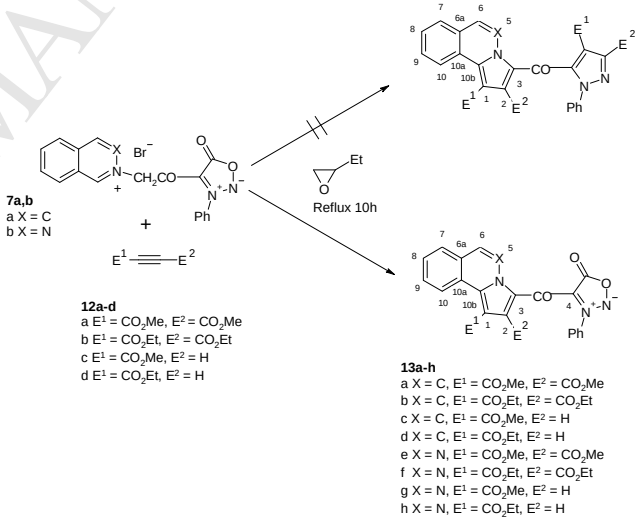
8 **9** **10** **11** **6**

Scheme 2. Synthesis of 4-bromoacetyl-3-phenylsydnone **6**.

The structure of the azinium bromides **7a,b** was assigned by ATR-IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. The ATR-IR spectral features are the presence of vibrational bands of the C=O groups at 1681 and 1678 cm^{-1} respectively for CO-CH_2, whereas the bands for the carbonyl groups of the sydnone ring appear at 1776 and 1782 cm^{-1} respectively. In the ^{1}H-NMR spectra of **7a,b** the methylene groups appear as deshielded singlets with δ of 6.46 ppm and 6.48 respectively due to their direct bonding to the quaternary nitrogen and C=O group. The ^{13}C-NMR spectrum for the azinium bromides presents all the expected signals. The characteristic shifts for the carbonylic atoms are at ~ 167 ppm for the endocyclic C=O of the sydnone ring and at ~176 ppm for the exocyclic C=O. The carbon atoms of the methylene groups appear at ~ 66 and 69 ppm, respectively. The C-1 carbons are strongly deshielded at ~ 150 ppm due to their proximity to the nitrogen atom.

*2.2. Reactions of bromides **7a,b** with alkynes*

The reaction of the sydnone-*N*-ylides (Scheme 3) was carried out by refluxing the bromides **7** with acetylenic dipolarophiles **12** in 1,2-epoxybutane. The latter solvent was employed both as reaction medium and for its ability to act as a base to generate the *N*-ylide from quaternary bromide **7**. One of the advantages of using 1,2-epoxybutane rather than other solvents and bases is the atom economy owing to the fact that the products of the reaction are only aromatized cycloadducts **13**. With other solvents and bases, the compounds **13** were obtained together with their corresponding dihydroderivatives **17**.[34-36,47,50,54,55]



7a,b
a X = C
b X = N

12a-d
a E^1 = CO_2Me, E^2 = CO_2Me
b E^1 = CO_2Et, E^2 = CO_2Et
c E^1 = CO_2Me, E^2 = H
d E^1 = CO_2Et, E^2 = H

13a-h
a X = C, E^1 = CO_2Me, E^2 = CO_2Me
b X = C, E^1 = CO_2Et, E^2 = CO_2Et
c X = C, E^1 = CO_2Me, E^2 = H
d X = C, E^1 = CO_2Et, E^2 = H
e X = N, E^1 = CO_2Me, E^2 = CO_2Me
f X = N, E^1 = CO_2Et, E^2 = CO_2Et
g X = N, E^1 = CO_2Me, E^2 = H
h X = N, E^1 = CO_2Et, E^2 = H

Scheme 3. Synthesis of hybrid structures **13a-h**.

In order to investigate the reactivity of sydnone-*N*-ylides towards acetylenic dipolarophiles the cycloaddition reactions were performed with large excess of acetylenic dipolarophiles and prolonged reaction time (e.g. under reflux in 1,2-epoxybutane for 48 h). Careful investigation by NMR spectroscopy of the crude reaction product indicated that in all cases, no compound resulted from 1,3-dipolar cycloaddition of the sydnone moiety and the acetylenic dipolarophiles. Instead, the formation of compounds **13** was a result of 1,3-dipolar cycloaddition of the *N*-ylide 1,3-dipole and the acetylenic dipolarophiles, demonstrating that under the reaction conditions reported, the sydnone 1,3-dipole is not sufficiently reactive.

2.3. Structural characterization of compounds 13

The structures of the *N*-hybrid heterocycles **13a-h** were confirmed by elemental analysis, as well as IR and NMR spectroscopy, and for one representative case (**13c**) by X-ray analysis (see below). The NMR data confirm the proposed structures for the cycloadducts **13a-h**. Additional evidence was obtained using heteronuclear correlation spectroscopy (HETCOR) and ^{1}H-^{1}H COSY.

The proton H-2 is present as a strongly deshielded singlet in the range 8.16-8.50 ppm. This is present only when the acetylenic dipolarophile **12** is a terminal alkyne. The H-10 proton is strongly deshielded with a shift in the range 8.52-9.85 ppm and this is good evidence that the ester group is attached to C-1 of the pyrrole ring, thus highlighting the regioselectivity of the cycloaddition reaction.

The chemical shifts of C-1 from the pyrroloazine moiety and C-4 from the sydnone ring are shielded and appear in the range 107.6–111.7 ppm. The ester groups are deshielded in the range 164.1–165.0 ppm. The chemical shift of the carbonyl group of the sydnone ring was found to be 164.8–166.1 ppm and was deduced by comparison with those from the starting material **6** and literature data.[53] The carbonyl group between the pyrroloazine and sydnone heterocycles is strongly deshielded, appearing at 168.8–170.9 ppm.

2.4. X-Ray structural confirmation

The X-ray structure of **13c**, as a representative member of the new hybrid heterocyclic series resulting from the cycloaddition of the sydnone-*N*-ylide, is shown in Figure 3 and a summary of the crystal and refinement data is provided in section 4.5. Full details appear in the CIF file (Supplementary material). Bond lengths associated with the 1,2,3-oxadiazole ring in **13c** are typical of those reported in the crystallographic literature for the sydnone moiety.[56] In particular, those in the molecule of **13c** (listed in the caption to Figure 3) are in close agreement with the corresponding lengths recently reported for 4-bromoacetyl-3-phenylsydnone.[57] Regarding the planarity of the 1,2,3-oxadiazole ring in **13c**, the maximum deviation of any of the five atoms from the least-squares plane is 0.006(1) Å. The 13-membered pyrroloisoquinoline system is very slightly bowed, with a maximum atomic deviation of 0.075(1) Å and this moiety is inclined at an angle of 32.8(1)° to the 1,2,3-oxadiazole ring. The orientations of the remaining residues (phenyl ring C26-C31 and the -CO-OCH$_3$ substituent) are evident from the torsion angles C20-N25-C26-C27 [70.6(2)°], C4-C3-C14-O16 [-23.2(2)°] and C3-C14-O16-C17 [177.4(1)°]. The overall molecular conformation of **13c** is largely determined by the intramolecular C-H···O hydrogen bonds shown in Figure 3. For these,the C···O and H···O distance pairs are as follows: C6-H···O19 [2.835(1), 2.22 Å], C11-H···O15 [2.980(2), 2.18 Å] and C4-H···O22 [3.047(1), 2.40 Å]. The reported values are all significantly less than the corresponding sums of the van der Waals radii (C···O 3.22, H···O 2.72 Å,).[58]

Molecules of **13c** associate as centrosymmetric dimers *via* intermolecular C-H···O hydrogen bonding and further crystal cohesion is effected by π-stacking of inversion-related pyrroloisoquinoline units with closest approach 3.528(1) Å.

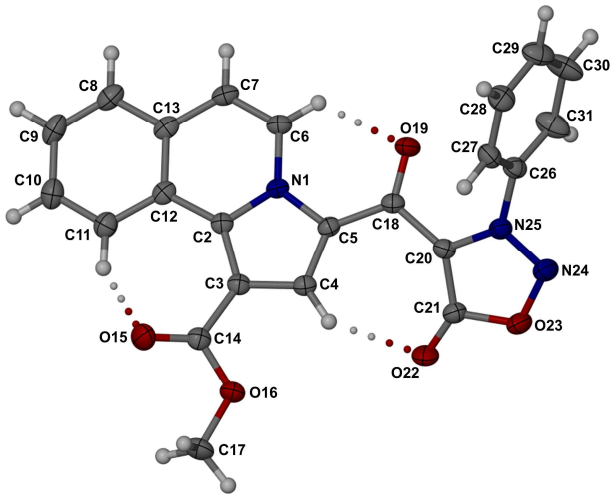
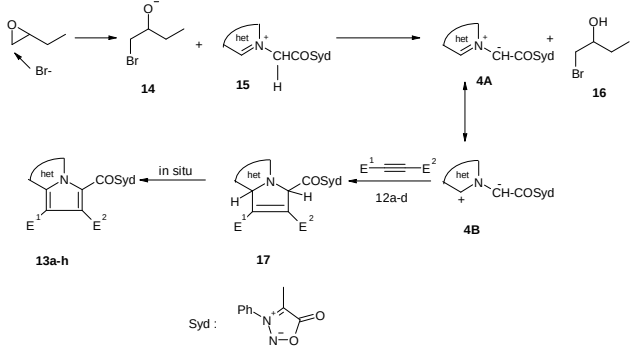


Fig. 3. The X-ray structure of **13c**. Thermal ellipsoids are drawn at the 50% probability level and intramolecular C-H···O hydrogen bonds are indicated as dotted lines. Bond lengths in the sydnone moiety are C20-C21 1.420(2), C21-O23 1.424(1), O23-N24 1.370(1), N24-N25 1.301(1), N25-C20 1.360(1), C21-O22 1.207(1) Å.

2.5. Mechanistic considerations

The reaction mechanism for obtaining hybrid heterocycles **13** (Scheme 4) implies, in the first step, the opening of the 1,2-epoxybutane ring by the reaction with the bromide ion to form the alkoxide **14**, which abstracts the methylene proton, generating the *N*-ylide **4** *in situ*. In the next step, the *N*-ylide reacts with the acetylenic dipolarophiles **12a-d** to form the primary cycloadduct **17**, which undergoes aromatization to yield the final cycloadducts **13a-h**.



Scheme 4. Reaction mechanism of 1,3-dipolar cycloaddition.

3. Conclusions

In conclusion, the *bis*-1,3-dipolar structures **4**, incorporating both sydnone and *N*-heteroaromatic *N*-ylides (isoquinolinium and phthalazinium *N*-ylides) in the same molecule, reacted by reflux in 1,2-epoxybutane with acetylenic dipolarophiles to form pyrroloazines with a sydnone moiety **13**. The compounds **13** resulted from 1,3-dipolar cycloaddition of the acetylenes with the *N*-ylide 1,3-dipole preferentially, owing to the lack of reactivity

of the sydnone 1,3-dipole under the reported experimental conditions. The synthesis of the new compounds represents an easy access to 4-hetaroyl-sydnones (Het-CO-Sydnones), compounds that to our knowledge are not reported in the literature. The aroylation of sydnones at the 4 position is otherwise difficult to achieve. The structure of the new hybrid heterocycles **13** was assigned by elemental analysis, ATR-IR, NMR spectroscopy and for one case was confirmed by X-ray analysis. In addition, a one-step method for the synthesis of 4-acetyl-3-phenylsydnone **11** was developed starting from *N*-nitroso-*N*-phenylglycine **9** and acetic anhydride. The new method circumvents isolation of 3-phenylsydnone and its subsequent acetylation.

4. Experimental

4.1. General

Melting points were determined on a Boëtius hot plate microscope. The IR spectra were recorded on a FT-IR Bruker Vertex 70. The NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for ^{1}H-NMR and 75 MHz for ^{13}C-NMR. Supplementary evidence was given by HETCOR and COSY experiments. Structural elucidation was achieved by X-ray diffraction analysis of a representative compound.

*4.2. General procedure for synthesis of azine bromides **7a,b***

To a solution of **6** (1.98 g, 7 mmol) (4-bromoacetyl-3-phenylsydnone) in 25 mL of acetone was added 5**a,b** (7 mmol). The solution was heated at reflux with stirring for 4 h and after cooling the precipitate was filtered and washed with acetone. The crude product was used without further purification.

*4.2.1. 2-[2-(3-Phenylsydnon-4-yl)-2-oxoethyl]isoquinolinium bromide (**7a**)*: The compound was purified by crystallization from ethanol, yield 87%, mp 245-246 ºC. Found C, 55.67; H, 3.67; N, 10.47. $C_{19}H_{14}BrN_3O_3$ requires C, 55.36; H, 3.42; N, 10.19. IR, (ATR): 1776 cm^{-1} ($\nu_{C=O}$ endocyclic); 1681 cm^{-1} ($\nu_{C=O}$ exocyclic). ^{1}H NMR (300 MHz, $CDCl_3$ + TFA) δ (ppm): 6.46 (s, 2H, CH_2), 7.52-7.57, 7.60-7.67 (2m, 5H, Ph), 7.96-8.02, 8.12-8.22, 8.41-8.44 (3m, 4H, H-5,H-6, H-7, H-8), 8.28 (d, 1H, *J* = 6.9 Hz, H-4), 8.46 (d, 1H, *J* = 6.9 Hz, H-3), 9.76 (s, 1H, H-1). ^{13}C NMR (75 MHz, $CDCl_3$ + TFA) δ (ppm): 66.6 (CH_2), 105.3 (C-4,Syd), 125.0 (2C, *o*-Ph), 126.2, 127.3, 131.1, 133.3, 135.8, 138.3 (C-3, C-4, C-5, C-6, C-7, C-8), 127.7, 138.2 (C-4a, C-8a), 129.8 (2C, *m*-Ph), 131.9 (*p*-Ph), 134.0 (C-1, Ph), 151.3 (C-1), 167.4 (CO-endocyclic), 176.3 (CO-exocyclic).

*4.2.2. 2-[2-(3-Phenylsydnon-4-yl)-2-oxoethyl]phthalazinium bromide (**7b**)*: The compound was purified by crystallization from a mixture of ethanol and acetonitrile (3:1), yield 85%, mp 231-234 ºC Found: C, 52.69; H, 3.36; N, 13.82. $C_{18}H_{13}BrN_4O_3$ requires C, 52.32; H, 3.17; N, 13.56. IR (ATR): 1782 cm^{-1} ($\nu_{C=O}$ endocyclic); 1678 cm^{-1} ($\nu_{C=O}$ exocyclic). ^{1}H NMR (300 MHz, $CDCl_3$ + TFA) δ (ppm): 6.48 (s, 2H, CH_2), 7.49-7.63 (m, 5H, Ph), 8.28-8.34 (m, 2H, H-6, H-7), 8.40-8.45, 8.69-8.71 (2m, 2H, H-5, H-8), 9.56 (s, 1H, H-4); 10.64 (s, 1H, H1). ^{13}C NMR (75 MHz, $CDCl_3$ + TFA) δ (ppm): 69.3 (CH_2), 105.3 (C4-Syd), 124.9 (2C, *o*-Ph), 127.8, 128.0 (C-4a, C-8a), 127.9, 133.3, (C-5, C-8), 129.8 (2C, *m*-Ph), 131.9 (C, *p*-Ph), 133.9 (C-1, Ph), 136.9, 140.6 (C-6, C-7), 153.9, 154.2 (C-1, C-4), 167.1 (CO-endocyclic), 175.6 (CO-exocyclic).

*4.3 General procedure for the synthesis of pyrrolo[2,1-a]azines **13a-h***

To a suspension of **7** (3 mmol) in 10 mL of 1,2-epoxybutane was added **12** (4 mmol). The reaction mixture was heated at reflux with stirring for 10 h when a solution was obtained. The solvent was evaporated in vacuum and the residue was treated with methanol or ethanol. The yellow precipitate was filtered by suction and washed with methanol or ethanol. The product was purified by crystallization from an appropriate solvent.

*4.3.1. Dimethyl 3-[(3-phenylsydnon-4-yl)-oxomethyl]-pyrrolo[2,1-a]isoquinoline-1,2-dicarboxylate (**13a**)*: The compound was purified by crystallization from acetonitrile-ethanol (1:1), yield 48%, mp 171-173 ºC. Found: C, 63.77; H, 3.91; N, 9.15. $C_{25}H_{17}N_3O_7$ requires C, 63.70; H, 3.63; N, 8.91. IR (ATR): 1760 cm^{-1} ($\nu_{C=O}$ endocyclic); 1711 cm^{-1} ($\nu_{C=O}$ exocyclic). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.90, 3.99 (2s, 6H, 2Me), 7.03 (d, 1H, *J* = 7.4 Hz, H-6), 7.52-7.75 (m, 8H, H-7, H-8, H-9, H-2', H-3', H-4', H-5', H-6'), 8.52-8.55 (m, 1H, H-10), 8.65 (d, 1H, *J* = 7.4 Hz, H-5). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 52.8, 53.0 (2Me), 109.0, 111.4 (C-1, C-4syd), 116.2 (C-6), 122.2, 124.0, 126.5, 129.5, 132.3 (C-2, C-3, C-6a, C-10a, C-10b), 123.4 (C-5), 124.3 (C-2', C-6'), 125.0 (C-10), 127.2, 128.5, 129.2 (C-7, C-8, C-9), 129.8 (C-3', C-5'), 132.4 (C-4'), 135.0 (C-1'), 164.8, 164.9 (2COO), 166.1 (CO-endocyclic), 170.6 (CO-exocyclic).

*4.3.2. Diethyl 3-[(3-phenylsydnon-4-yl)-oxomethyl]-pyrrolo[2,1-a]isoquinoline-1,2-dicarboxylate (**13b**)*: The compound was purified by crystallization from acetonitrile-ethanol (1:1), yield 53%, mp 139-141 ºC. Found: C, 64.71; H, 4.51; N, 8.69. $C_{27}H_{21}N_3O_7$ requires C, 64.93; H, 4.24; N, 8.41. IR (ATR): 1763 cm^{-1} ($\nu_{C=O}$ endocyclic); 1716 cm^{-1} ($\nu_{C=O}$ exocyclic). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.38, 1.43 (2t, 6H, *J* = 7.4 Hz, 2Me), 4.34, 4.48 (2q, 4H, *J* = 7.4 Hz, $2CH_2$), 7.06 (d, 1H, *J* = 7.7 Hz, H-6), 7.56-7.76 (m, 8H, H-7, H-8, H-9, H-2', H-3', H-4', H-5', H-6'), 8.55-8.58 (m, 1H, H-10), 8.70 (d, 1H, *J* = 7.7 Hz, H-5). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 14.1, 14.2 (2Me), 61.9, 62.1 ($2CH_2$), 109.2. 112.1 (C-1, C-4syd), 116.2 (C-6), 122.3, 124.3 126.9, 129.7 132.5 (C-2, C-3, C-6a, C-10a, C-10b), 123.6 (C-5), 124.4 (C-2', C-6'), 125.2 (C-10), 127.3, 128.6, 129.2 (C-7, C-8, C-9), 129.9 (C-3', C-5'), 132.4 (C-4'), 135.1 (C-1'), 164.5, 165.0 (2COO), 165.9 (CO-endocyclic), 170.9 (CO-exocyclic).

*4.3.3. Methyl 3-[(3-phenylsydnon-4-yl)-oxomethyl]-pyrrolo[2,1-a]isoquinoline-1-carboxylate (**13c**)*: The compound was purified by crystallization from acetonitrile, yield 43%, mp 227-228 ºC. Found: C, 67.11; H, 3.87; N, 10.44. $C_{23}H_{15}N_3O_5$ requires C, 66.83; H, 3.66; N, 10.16. IR (ATR): 1758 cm^{-1} ($\nu_{C=O}$ endocyclic); 1700 cm^{-1} ($\nu_{C=O}$ exocyclic). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.88 (s, 3H, Me), 7.06 (d, 1H, *J* = 7.4 Hz, H-6), 7.48-7.62 (m, 8H, H-7, H-8, H-9, H-2', H-3', H-4', H-5', H-6'), 8.41 (s, 1H, H-2), 9.22 (d, 1H, *J* = 7.4 Hz, H-5), 9.73-9.76 (m, 1H, H-10). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 52.1 (Me), 107.6, 111.1 (C-1, C-4syd), 116.0 (C-6), 122.3, 124.5, 130.9, 138.0 (C-3, C-6a, C-10a, C-10b), 124.2 (C-2', C-6'), 124.7 (C-5), 126.7, 128.1, 129.8 (C-7, C-8, C-9), 128.4 (C-10), 129.9 (C-3', C-5'), 130.5 (C-2), 132.4 (C-4'), 135.4 (C-1'), 164.8 (COO), 165.6 (CO-endocyclic), 169.0 (CO-exocyclic).

*4.3.4. Ethyl 3-[(3-phenylsydnon-4-yl)-oxomethyl]-pyrrolo[2,1-a]isoquinoline-1-carboxylate (**13d**)*: The compound was purified by crystallization from acetonitrile, yield 47%, mp 199-201 ºC. Found: C, 67.74; H, 4.29; N, 10.12. $C_{24}H_{17}N_3O_5$ requires C, 67.44; H, 4.01; N, 9.83. IR (ATR): 1755 cm^{-1} ($\nu_{C=O}$ endocyclic); 1701 cm^{-1} ($\nu_{C=O}$ exocyclic). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.48 (t, 3H, *J* = 7.1 Hz, Me), 4.46 (q, 2H, *J* = 7.1 Hz, CH_2), 7.17 (d, 1H, *J* = 7.4 Hz, H-6), 7.59-7.78 (m, 8H, H-7, H-8, H-9, H-2',

H-3', H-4', H-5', H-6'), 8.50 (s, 1H, H-6), 9.34 (d, 1H, *J* = 7.4 Hz, H-5), 9.84-9.87 (m, 1H, H-10). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 14.6 (Me), 61.0 (CH_2), 107.7, 111.7 (C-1, C-4 syd), 116.0 (C-6), 122.3, 124.6, 131.0, 138.1 (C-3, C-6a, C-10a, C-10b), 124.3 (C-2', C-6'), 124.9 (C-5), 126.8, 128.2, 129.8 (C-7, C-8, C-9), 128.6 (C-10), 129.9 (C-3', C-5'), 130.5 (C-2), 132.4 (C-4'), 135.4 (C-1'), 164.5 (COO), 165.6 (CO-endocyclic), 169.1 (CO-exocyclic).

*4.3.5. Dimethyl 3-[(3-phenylsydnon-4-yl)-oxomethyl]-pyrrolo[2,1-a]phthalazine-1,2-dicarboxylate (**13e**)*: The compound was purified by crystallization from acetonitrile and ethanol (1:1), yield 54%, mp 214-215 ºC. Found: C, 61.31; H, 3.65; N, 11.88. $C_{24}H_{16}N_4O_7$ (472) requires C, 61.02; H, 3.41; N, 11.68. IR (ATR): 1726 cm^{-1} ($\nu_{C=O}$ endocyclic), 1709 cm^{-1} ($\nu_{C=O}$ exocyclic). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.87 (s, 3H, Me), 3.95 (s, 3H, Me), 7.54-7.69 (m, 6H, H-8, H-2', H-3', H-4', H-5', H-6'), 7.80-7.85 (m, 2H, H-7, H-9), 8.54 (s, 1H, H-6), 8.96-8.99 (m, 1H, H-10). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 52.6 (Me), 52.8 (Me), 108.0, 108.2 (C-1, C-4syd), 121.6, 122.5, 125.9, 126.7, 126.8 (C-2, C-3, C-6a, C-10a, C-10b), 124.6 (C-2', C-6'), 125.6 (C-10), 128.3 (C-7), 129.6 (C-8), 129.7 (C-3', C-5'), 132.5 (C-4'), 133.6 (C-9), 134.8 (C-1'), 147.1 (C-6), 164.6, 164.7 (2COO), 165.1 (CO-endocyclic), 170.2 (CO-exocyclic).

*4.3.6. Diethyl 3-[(3-phenylsydnon-4-yl)-oxomethyl]-pyrrolo[2,1-a]phthalazine-1,2-dicarboxylate (**13f**)*: The compound was purified by crystallization from ethyl acetate, yield 56%, mp 134-136 ºC. Found: C, 62.64; H, 4.31; N, 11.42. $C_{26}H_{20}N_4O_7$ requires C, 62.40; H, 4.03; N, 11.19. IR (ATR): 1763 cm^{-1} ($\nu_{C=O}$ endocyclic); 1706 cm^{-1} ($\nu_{C=O}$ exocyclic). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.26, 1.33 (2t, 6H, *J* = 7.1 Hz, 2Me), 4.28, 4.36 (2q, 4H, *J* = 7.1 Hz, 2CH_2), 7.46-7.63 (m, 6H, H-8, H-2', H-3', H-4', H-5', H-6'), 7.73-7.79 (m, 2H, H-7, H-9), 8.46 (s, 1H, H-6), 8.88-8.91 (m, 1H, H-10). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 14.1, 14.2 (2Me), 61.7, 61.8 (2CH_2), 108.4, 108.5 (C-1, C-4syd), 121.7, 122.7, 125.7, 126.7, 126.8 (C-2, C-3, C-6a, C-10a, C-10b), 124.6 (C-2', C-6'), 125.6 (C-10), 128.3 (C-7), 129.5 (C-8), 129.7 (C-3', C-5'), 132.5 (C-4'), 133.5 (C-9), 134.9 (C-1'), 147.0 (C-6), 164.1 (COO), 164.8 (COO, CO-endocyclic), 170.3 (CO-exocyclic).

*4.3.7. Methyl 3-[(3-phenylsydnon-4-yl)-oxomethyl]-pyrrolo[2,1-a]phthalazine-1-carboxylate (**13g**)*: The compound was purified by crystallization from nitromethane, yield 48%, mp 244-246 ºC. Found: C, 64.13; H, 3.65; N, 13.76. $C_{22}H_{14}N_4O_5$ requires C, 63.77; H, 3.41; N, 13.52. IR (ATR): 1776 cm^{-1} ($\nu_{C=O}$ endocyclic); 1709 cm^{-1} ($\nu_{C=O}$ exocyclic). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.97 (s, 3H, Me), 7.55-7.78 (m, 6H, H-8, H-2', H-3', H-4', H-5', H-6'), 7.86-7.94 (m, 2H, H-7, H-9), 8.18 (s, 1H, H-2), 8.68 (s, 1H, H-6), 9.84-9.87 (m, 1H, H-10). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 52.1 (Me), 107.9, 109.1 (C-1, C-4syd), 122.4, 126.2, 126.8, 131.0 (C-3, C-6a, C-10a, C-10b), 124.6 (C-2', C-6'), 124.8 (C-2), 127.7, 127.9, 130.2 (C-7, C-8, C-10), 129.8 (C-3', C-5'), 132.3 (C-4'), 133.3 (C-9), 135.3 (C-1'), 146.6 (C-6), 164.5 (COO), 165.3 (CO-endocyclic), 168.8 (CO-exocyclic).

*4.3.8. Ethyl 3-[(3-phenylsydnon-4-yl)-oxomethyl]-pyrrolo[2,1-a]phthalazine-1-carboxylate (**13h**)*: The compound was purified by crystallization from nitromethane, yield 44%, mp 234-236 ºC. Found: C, 64.76; H, 4.02; N, 13.34. $C_{23}H_{16}N_4O_5$ requires C, 64.48; H, 3.76; N, 13.08. IR (ATR): 1763 cm^{-1} ($\nu_{C=O}$ endocyclic); 1704 cm^{-1} ($\nu_{C=O}$ exocyclic). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.45 (t, 3H, *J* = 7.1 Hz, Me), 4.43 (q, 2H, *J* = 7.1 Hz, CH_2), 7.55-7.65 (m, 6H, H-8, H-2', H-3', H-4', H-5', H-6'), 7.84-7.93 (m, 2H, H-7, H-9), 8.16 (s, 1H, H-2), 8.65 (s, 1H, H-6), 9.82-9.85 (m, 1H, H-10). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 14.6 (Me), 61.0 (CH_2), 108.0, 109.6 (C-1, C-4syd), 122.3, 126.3, 126.8, 130.8 (C-3, C-6a, C-10a, C-10b), 124.6 (C-2', C-6'), 124.8 (C-2), 127.7, 127.9, 130.1 (C-7, C-8, C-10), 129.8 (C-3', C-5'), 132.3 (C-4'), 133.2 (C-9), 135.3 (C-1'), 146.5 (C-6), 164.1 (COO), 165.2 (CO-endocyclic), 168.9 (CO-exocyclic).

*4.4. Procedure for the synthesis of 4-acetyl-3-phenylsydnone (**11**)*

A solution of **9** (10 g, 55 mmol) in 30 mL of acetic anhydride was stirred until dissolution occurred and then was kept at room temperature for 24 h. The solution was then cooled on an ice bath and perchloric acid 60% (1.5 mL) was added dropwise. The reaction was stirred for 12 h and the reaction mixture was poured into cold water and then neutralized with (ca. 10 g) sodium carbonate. The precipitate was filtered and washed with water on the filter and the compound **11** was dried at room temperature.

*4.5. Crystal and refinement data for **13c***

The X-ray structure of **13c** was determined by direct methods and refined by full-matrix least-squares, as detailed in the CIF file (Supplementary Material). A summary of the salient data is as follows: $C_{23}H_{15}N_3O_5$, M = 413.38, 0.32 × 0.18 × 0.17 mm^3, monoclinic, space group $P2_1/n$ (No. 14), a = 11.2661(2), b = 8.1641(2), c = 20.8189(4) Å, β = 94.320(1)°, V = 1909.43(7) Å^3, Z = 4, D_c = 1.438 g/cm^3, F_{000} = 856, MoKα radiation, λ = 0.71073 Å, T = 173(2)K, $2\theta_{max}$ = 56.6º, 9111 reflections collected, 4724 unique (R_{int} = 0.0223). Final *GooF* = 1.032, *R1* = 0.0370, *wR2* = 0.0954, *R* indices based on 3650 reflections with I >2σ(I) (refinement on F^2), 282 parameters, 0 restraints, CCDC no. 1404872.

Acknowledgements

M.R.C. thanks the University of Cape Town and the NRF (Pretoria) for research support. Any opinion, findings and conclusions or recommendations expressed in this material are those of the author and therefore the NRF does not accept any liability in that regard.

References and notes

1. Earl, J. C.; Mackney, A. W. *J. Chem. Soc*. **1935**, 899-900.
2. Baker, W.; Ollis, W. D. *Quart. Rev. (London)* **1957**, *11*, 15-29.
3. Hedge, J. C.; Girish, K. S.; Adhikari, A.; Kalluraya, B. *Synth. Commun.* **2013**, *43*, 301-308.
4. Asundaria, S. T.; Patel, K. C. *Pharm. Chem. J.* **2012**, *45*, 725-731.
5. Asundaria, S. T.; Pannecouque, C.; De Clercq, E.; Supuran, C. T.; Patel, K. C. *Med. Chem. Res.* **2013**, *22*, 5752-5763.
6. Bansode, S.; Kamble, R. *Med. Chem. Res.* **2012**, *21*, 867-873.
7. Tegginamath, G.; Kamble, R.; Taj, T.; Kattimani, P. P.; Meti, G. Y. *Med. Chem. Res.* **2013**, *22*, 4367-4375.
8. Asundaria, S. T.; Pannecouque, C.; De Clercq, E.; Patel, K. C. *Pharm. Chem. J.* **2014**, *48*, 260-268.
9. Nithinchandra Kalluraya, B.; Aamir, S.; Shabaraya, A. R. *Eur. J. Med. Chem.* **2012**, *54*, 597-604.
10. Browne, D. L.; Harrity, J. P. A. *Tetrahedron* **2010**, *66*, 533-568.
11. Dumitrascu, F.; Mitan, C. I.; Dumitrescu, D.; Draghici, C.; Caproiu, M. T. *Arkivoc* **2002**, (*ii*), 80-86.
12. Dumitrascu, F.; Draghici, C.; Dumitrescu, D.; Tarko, L.; Raileanu, D. *Liebigs Ann./Recueil* **1997**, 2613-2616.
13. Brown, D. C.; Turnbull. K. *Synth. Commun.* **2013**, *23*, 3233-3237.
14. Tien, H. J.; Yeh, J. C.; Wu, S. J. *J. Chin. Chem. Soc*. **1992**, *39*, 443-447.
15. Huisgen, R.; Grashley, R.; Gotthardt, H.; Schmidt, R. *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 48-49.
16. Dürüst. Y.; Sağırlı, A.; Kariuki, B. M.; Knight, D. W. *Tetrahedron* **2014**, *35*, 6012-6019.
17. Delaunay, T.; Es-Sayed, M.; Vors, J-P.; Monteiro, N.; Balme, G. *Eur. J. Org. Chem.* **2011**, 3837–3848.
18. Chang, E. C.; Wen, Y. L.; Chang, C. H.; Shen, Y. H.; Wen, S. B.; Yeh, M. Y.; Wong, F. F. *Tetrahedron* **2012**, *68*, 5920-5924.

19. Foster, R. S.; Jakobi, H.; Harrity, J. P. A. *Tetrahedron Lett.* **2011**, *52*, 1506-1508.
20. Specklin, S.; Decuypere, E.; Plougastel, L.; Aliani, S.; Taran, F. *J. Org. Chem.* **2014**, *79*, 7772-7777.
21. Kolodych, S.; Rasolofonjatovo, E.; Chaumontet, M.; Nevers, M-C.; Creminon, C.; Taran, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 1-6.
22. Foster, R. S.; Huang, J.; Vivat, J. F.; Browne D. L.; Harrity, J. P. A. *Org. Biomol. Chem.* **2009**, *7*, 4052-4056.
23. Kuo, C. N.; Wang, S. P.; Yeh, M. Y.; Tien, H. J. *J. Chin. Chem. Soc.* **1992**, *39*, 641-645.
24. Bhosale, S. K.; Deshpande, S. R.; Wagh, R. D. *J. Chem. Pharm. Res.* **2012**, *4*, 1185-1199.
25. Mitsumori, T.; Bendikov, M.; Sedo, J.; Wudl, F, *Chem. Mater.* **2003**, *15*, 3759-3768.
26. Uff, B. C.; Ghaem-Maghami, G.; Budhram, R. S.; Wilson, C. L.; Apatu, J. O. *J. Heterocycl. Chem.* **1989**, *26*, 571-576.
27. Butnariu, R. M.; Caprosu, M. D.; Bejan, V.; Ungureanu, M.; Poiata, A.; Florescu, C. M.; Mangalagiu, I. I. *J. Heterocycl. Chem.* **2007**, *44*, 1149-1152.
28. Denislamova, E. S.; Shklyaev, Y. V.; Makhmudov, R. R.; Maslivets, A. N. *Pharm. Chem. J.* **2012**, *46*, 551-552.
29. Moreno, L.; Párraga, J.; Galán, A.; Cabed, N.; Prim, J.; Cortes, D. *Bioorg. Med. Chem.* **2012**, *20*, 6589–6597.
30. Muthusaravana, S.; Peruma, S.; Yogeeswar, P.; Sriram, D. *Tetrahedron Lett.* **2010**, *51*, 6439–6443.
31. Cheng, Y.; Ma, B.; Wudl, F. *J. Mater. Chem.* **1999**, *9*, 2183–2188.
32. Zbancioc, G. N.; Huhn, T.; Grot, U.; Deleanu, C.; Mangalagiu, I. I. *Tetrahedron*, **2010**, *66*, 4298-4306.
33. Passler, U.; Knolker, H. In *The Alkaloids: Chemistry and Biology;* Knolker, H.; Ed. Elsevier Inc., 2011, vol. 70 , pp 79-151.
34. Dumitrascu, F.; Mitan, C. I.; Drăghici, C.; Căproiu, M. T.; Răileanu, D. *Tetrahedron Lett.* **2001**, *42*, 8379–8382.
35. Dumitrascu, F.; Drăghici, C.; Căproiu, M. T.; Dumitrescu, D.; Bădoiu, A. *Rev. Roum. Chim.* **2006**, *51*, 643–647.
36. Butler, R.N.; Coyne, A.G.; McArdle, P.; Cunningham, D.; Burke, L.A. *J. Chem. Soc. Perkin Trans. 1* **2001**, 1391–1397.
37. Caira, M. R.; Georgescu, E.; Georgescu, F.; Albotă, F.; Dumitrascu, F. *Monatsh. Chem.* **2011**, *142*, 743–748.
38. Zhou, J.; Hu, Y.; Hu, H. *J. Heterocycl. Chem.* **2000**, *37*, 1165-1168.
39. Sukhotin, A. V.; Kartsev, V. G.; Aleksandrov, Yu. A.; Dolgushin, F. M. *Russ. Chem. Bull. Int. Ed.* **2005**, *54*, 2437-2440.
40. Dumitrascu, F.; Căproiu, M. T.; Georgescu, F.; Drăghici, B.; Popa, M. M.; Georgescu, E. *Synlett* **2010**, 2407-2410.
41. An, J.; Yang, Q. Q.; Wang, Q.; Xiao, W. J. *Tetrahedron Lett.* **2013**, *54*, 3834–3837.
42. Agarwal, S.; Kataeva, O.; Schmidt U.; Knolker, H. *RSC Adv.* **2013**, *3*, 1089-1096.
43. Vila, C.; Lau, J.; Rueping, M. *Beilstein J. Org. Chem.* **2014**, *10*, 1233–1238.
44. Chen, J.; Xu, Q.; Liao, W. *Chem. Eur. J.* **2014**, *20*, 13876-13880.
45. Liu, Z.; Wu, L.; Sun, J.; Yan, C. *Chem. Res. Chinese U.* **2012**, *28*, 990-993.
46. Fan, X.; Wang, Y.; He, Y.; Guo, S.; Zhang, X. *Eur. J. Org. Chem.* **2014**, 713–717.
47. Dumitrascu, F.; Caira, M. R.; Georgescu, E.; Georgescu, F.; Drăghici, C.; Popa, M. M. *Heteroat. Chem.* **2011**, *22*. 723-729.
48. Huang, L.; Zhao, J. *Chem. Commun.* **2013**, *49*, 3751-3753.
49. Iza, A.; Ugarriza, I.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Tetrahedron* **2013**, *69*, 8878-8884.
50. Han, Y.; Hou, H.; Fu, Q.; Yan, C. *Tetrahedron* **2011**, *67*, 2313-2322.
51. Caira, M. R.; Popa, M. M.; Drăghici, C.; Barbu, L.; Dumitrescu, D.; Dumitrascu, F. *Tetrahedron Lett.* **2014**, *55*, 5635–5638.
52. Wu, L.; Sun, J.; Yan, C. *Chin. J. Chem.* **2012**, *30*, 590-596.
53. Tien, H.; Kanda, K.; Chinone, A.; Ohta, M. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3304-3306
54. Ruano, J. L. G.; Fraile, A.; Martín, M. R.; Gonzalez, G.; Fajardo, C.; Martín-Castro, A. M. *J. Org. Chem.* **2011**, *76*, 3296–3305.
55. Mondal, S.; Maity, A.; Paira, R.; Banerjee, M.; Bharitkar, Y. P.; Hazra, A.; Banerjee, S.; Mondal, N. B. *Tetrahedron Lett.* **2012**, *53*, 6288–6291.
56. Cambridge Structural Database and Cambridge Structural Database system, Version 5.36, Cambridge Crystallographic Data Centre, University Chemical Laboratory; Cambridge, England, 2014.
57. Fun, H.-K.; Chia, T. S.; Nithichandra; Kalluraya, B.; Shetty, S. *Acta Cryst.* **2012**. *E68*, o2103.
58. Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441-451.

Supplementary Material

Supplementary data associated with this article: Crystallographic Information File (CIF) for compound **13c**, listing crystal data, experimental and refinement details, and molecular parameters (bond lengths, bond angles and torsion angles).