
# N-Heterocyclic Carbene Catalyzed Tail-to-Tail Oligomerization of *N,N*-Dimethyl-acrylamide (DMAA) and the Search for the Stetter Reaction of DMAA with Benzaldehyde

Oue-artorn Rajachan, Mathias Paul, Veera Reddy Yatham, Jörg-M. Neudörfl, Kwanjai Kanokmedhakul, Somdej Kanokmedhakul, Albrecht Berkessel

PII: S0040-4039(15)30146-5
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.09.104
Reference: TETL 46776

To appear in: *Tetrahedron Letters*

Received Date: 25 July 2015
Revised Date: 21 September 2015
Accepted Date: 23 September 2015

Please cite this article as: Rajachan, O-a., Paul, M., Yatham, V.R., Neudörfl, Jörg-M., Kanokmedhakul, K., Kanokmedhakul, S., Berkessel, A., N-Heterocyclic Carbene Catalyzed Tail-to-Tail Oligomerization of *N,N*-Dimethyl-acrylamide (DMAA) and the Search for the Stetter Reaction of DMAA with Benzaldehyde, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.09.104

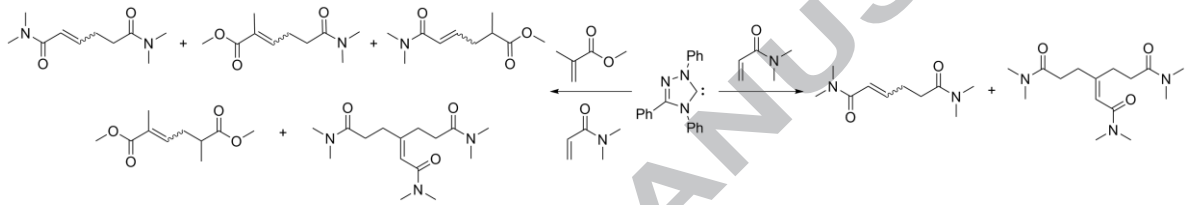
## Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

**N-Heterocyclic Carbene-Catalyzed Tail-to-Tail Oligomerization of *N,N*-Dimethyl-acrylamide (DMAA), and the Search for the Stetter Reaction of DMAA with Benzaldehyde**

Leave this area blank for abstract info.

Oue-artorn Rajachan, Mathias Paul, Veera Reddy Yatham, Jörg-M. Neudörfl, Kwanjai Kanokmedhakul, Somdej Kanokmedhakul, and Albrecht Berkessel*



Tetrahedron Letters
journal homepage: www.elsevier.com

# N-Heterocyclic Carbene Catalyzed Tail-to-Tail Oligomerization of *N,N*-Dimethyl-acrylamide (DMAA) and the Search for the Stetter Reaction of DMAA with Benzaldehyde

Oue-artorn Rajachan,[a] Mathias Paul,[b] Veera Reddy Yatham,[b] Jörg-M. Neudörfl,[b,c] Kwanjai Kanokmedhakul,[a] Somdej Kanokmedhakul,[a] and Albrecht Berkessel[b]*

[a]*Natural Products Research Unit, Department of Chemistry, and Center of Excellence for Innovation in Chemistry, Faculty of Science, Khon Kaen University, Khon Kaen, 40002, Thailand.*
[b]*Department of Chemistry, Cologne University, Greinstrasse 4, Cologne, 50939, Germany*
[c]*x-Ray crystallography, Cologne University, Greinstrasse 4, Cologne, 50939, Germany*

ARTICLE INFO

*Article history:*
Received
Received in revised form
Accepted
Available online

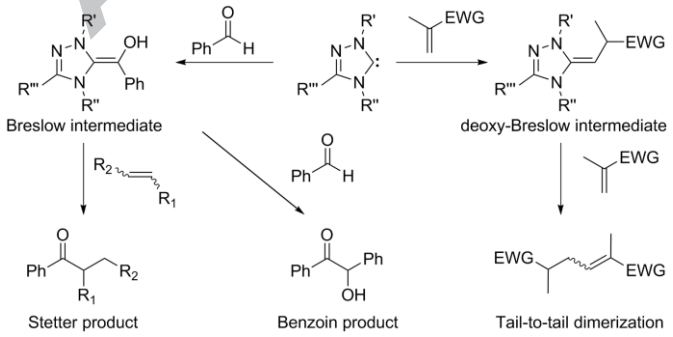
*Keywords:*
N-Heterocyclic carbene
Michael acceptor
Umpolung
Tail-to-tail oligomerization
Organocatalysis

ABSTRACT

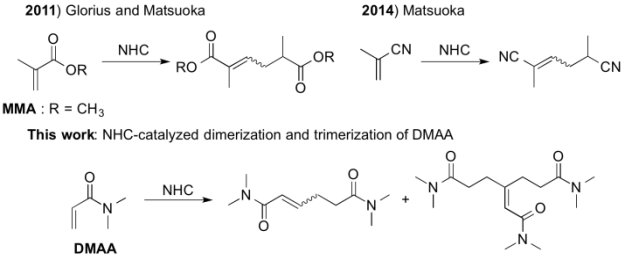
The tail-to-tail oligomerization of *N,N*-dimethylacrylamide catalyzed by N-heterocyclic carbenes (NHCs) was investigated, giving the dimerization and trimerization products in moderate combined yield. Reaction intermediates involved in the new oligomerization have been observed by NMR and ESI-MS. We showed the first NHC-catalyzed cross coupling of methyl methacrylate and *N,N*-dimethylacrylamide, and the reaction of benzaldehyde/benzoin with *N,N*-dimethylacrylamide.



The use of N-heterocyclic carbenes (NHCs) as organocatalysts[1] is based on their ability to invert the inherent polarity of functional groups. The Umpolung of aldehydes catalyzed by NHCs gives the Breslow intermediate[2] which can react with a second aldehyde to produce benzoin products,[3] and with a Michael system to form the Stetter products (Scheme 1).[4] Recently, the NHC-catalyzed Umpolung of Michael acceptors involving deoxy-Breslow intermediates has been developed. The first successful transformation was reported by Fu and co-workers, in the synthesis of cyclopentenones.[5] The groups of Glorius[6] and Matsuoka[7] have reported the tail-to-tail dimerization of several acrylate derivatives, e.g. methyl methacrylate (MMA, Scheme 2). In addition, the Matsuoka group also reported the NHC-catalyzed cyclotetramerization of acrylates.[8]




**Scheme 1**. Overview of NHC-catalyzed reactions of aldehydes and Michael systems.




**Scheme 2**. NHC-catalyzed tail-to-tail dimerization of acrylic acid derivatives.

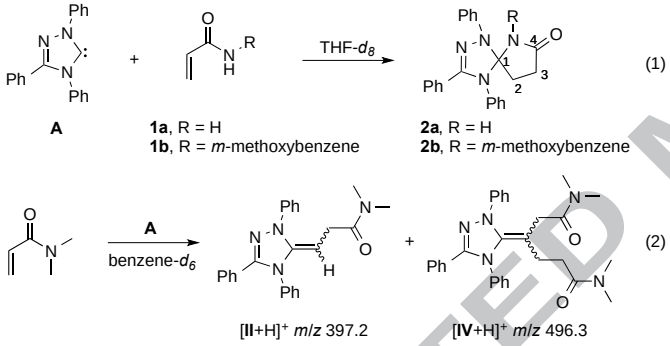
According to the literature, there is no report on the NHC-catalyzed tail-to-tail oligomerization of *N,N*-dimethylacrylamide (DMAA). There appears to be only one report on the catalytic dimerization of DMAA, which is metal-based. Sakakibara et al. reported the Ru catalyzed dimerization of DMAA, along with the formation of a small amount of a non-characterized trimer.[9]

In recent years, our group has studied intermediates of the NHC-catalyzed Umpolung of aldehydes.[10] Herein we report the tail-to-tail oligomerization of DMAA, the NHC-catalyzed cross coupling of DMAA with MMA, and the attempted Stetter reaction of benzaldehyde with DMAA.

* Corresponding author. Tel.: +49-221-470-3283; fax: +49-221-470-5102; e-mail: berkessel@uni-koeln.de

*I. Screening of the oligomerization of acrylamide derivatives in the presence of the triphenyl triazolylidene carbene **A***

First, we screened the reaction of acrylamides and the NHC **A** by NMR experiments (Scheme 3). The reaction of acrylamide (**1a**) and NHC **A** (2:1 molar ratio) in THF-$d_8$ was performed in an NMR tube and monitored by NMR spectroscopy. For the N-unsubstituted acrylamide **1a**, the spirocyclic lactam **2a** was observed. For example, characteristic $^1$H NMR signals of **2a** are a multiplet at δ=2.84-2.78 ppm (1H, H2b), a multiplet at δ=2.41-2.30 ppm (2H, H2a and H3b), and a multiplet at δ=1.96-1.91 ppm (1H, H3a). $^{13}$C NMR signals are 173.5 (C4), 99.5 (C1), 29.85 (C2), and 29.4 (C3). Analogously, the N-monosubstituted acrylamide **1b** (1:1 molar ratio) furnished the spiro-lactam **2b**. [Selected $^1$H NMR: 2.89-2.84 (m, 1H, H2b), 2.68-2.63 (m, 1H, H3b), 2.36-2.32 (m, 1H, H2a), 2.25-2.20 (m, 1H, H3a) and $^{13}$C NMR: 170.98 (1C, C4), 102.62 (1C, C1), 29.21 (1C, C3), and 27.12 (1C, C2)]. When DMAA was investigated in benzene-$d_6$ (1:1 molar ratio), NMR monitoring revealed a mixture of the *E*/*Z* isomers of the deoxy-Breslow intermediate **II** (Scheme 3), the second addition intermediate **IV** (Scheme 3), as well as the unreacted carbene. The ESI-MS analysis showed the corresponding peaks at *m*/*z*=397.2, *m*/*z*=496.3, and *m*/*z*=298.1, respectively. When two equivalent of DMAA were employed, instead only a mixture of the E/Z isomers of the secondary addition intermediate **IV** was observed.[11]



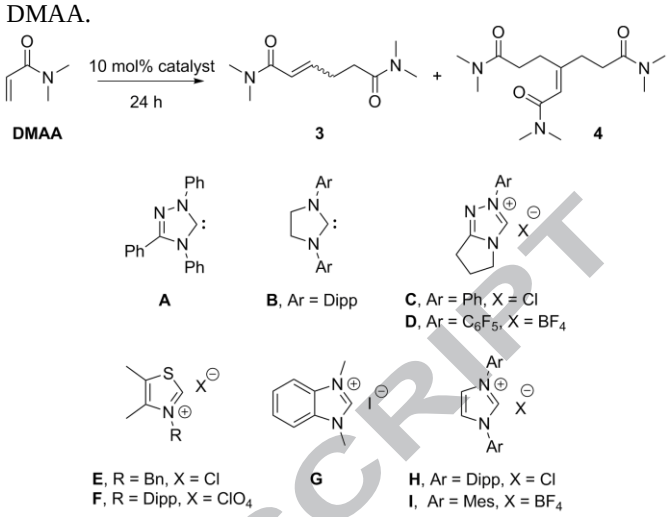

**Scheme 3.** The screening reaction of acrylamides catalyzed by **A**

Solvent effects on this reaction catalyzed by **A** are summarized in Table 1. Best results in the tail-to-tail oligomerization of DMAA were obtained when toluene was used as the solvent. The reaction was followed by GC and ESI-MS analysis, which showed that the reaction was not completed after 24 h (90 °C). The DMAA oligomerization could be completed at 105 °C within 24 h to give the dimer **3** in 47% yield with a 94:6 E/Z ratio and the trimer **4** in 11% isolated yield. When using THF as the solvent, the reaction generated **3** and **4** (20 and 9% yield) at 80 °C, and DMAA was recovered (12%). With other solvents, including DCE, DMSO, acetonitrile, or under solvent free conditions, no product formation was observed. We then investigated the catalytic activities of various NHCs and NHC precursors in the presence of DIPEA (di-*iso*-propylethylamine) at 105 °C in toluene. In contrast to carbene **A**, all other NHCs/ azolium salts **B**-**I** did not induce product formation.

*II. Proposed mechanism*

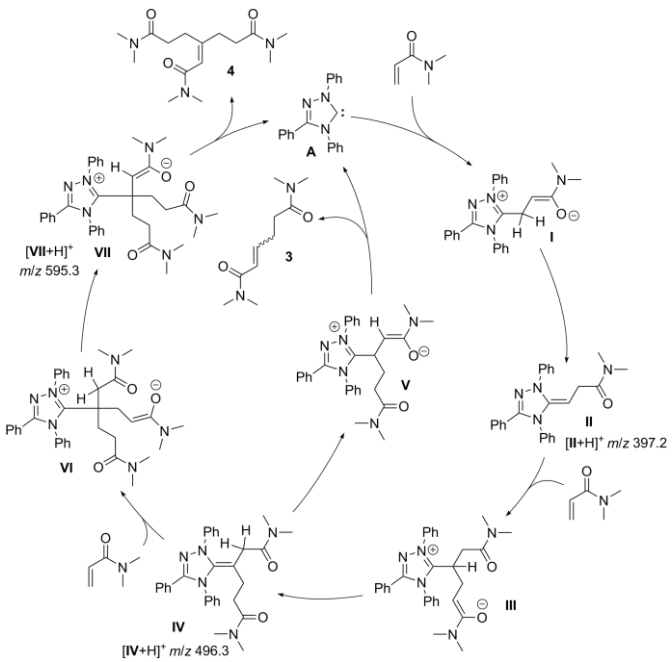
From the NMR and ESI-MS analyses, a reaction mechanism is proposed (Scheme 4). The addition of carbene **A** to the Michael acceptor DMAA generates the enolate **I**, followed by proton transfer to give the deoxy-Breslow intermediate **II**, which was detected by NMR spectroscopy and ESI-MS analysis (*m*/*z*=367.2). Addition of this intermediate **II** to a second molecule of DMAA leads to tail-to-tail dimerization, forming the intermediate **III**, and a second proton transfer gives the intermediate **IV** (detected by NMR and ESI-MS, *m*/*z* =496.3). A formal 1,2-proton shift in **IV** followed by elimination of NHC **A** from intermediate **V** gives the dimer **3**. Alternatively, intermediate **IV** can react with a third molecule of DMAA leading to the intermediate **VI**. Proton transfer in **VI** generates the intermediate **VII** (detected by ESI-MS, *m*/*z* =595.3). The elimination of carbene **A** from **VII** produces the DMAA trimer **4**.

**Table 1**. Optimization of the tail-to-tail oligomerization of DMAA.

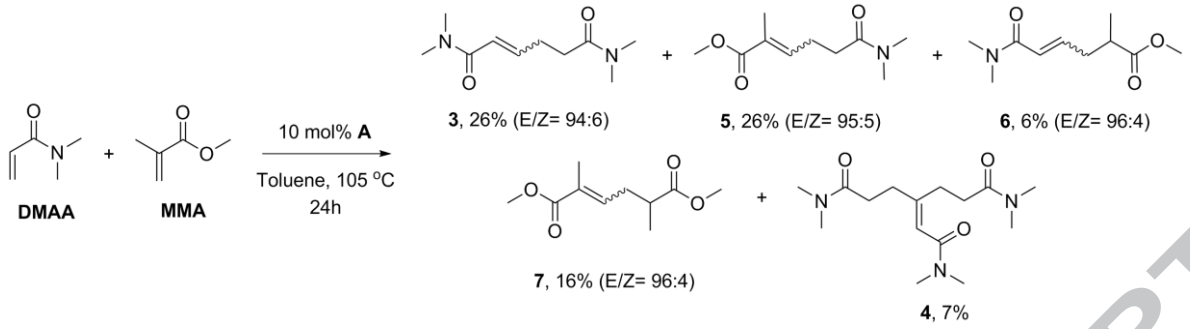



| entry | catalyst | solvent | temperature [°C] | yield [%] | | E/Z[a] |
|---|---|---|---|---|---|---|
| | | | | **3** | **4** | **3** |
| 1 | **A** | toluene | 105 | 46 | 11 | 94/6 |
| 2 | **A** | THF | 80 | 20 | 9 | 93/7 |
| 3 | **A** | DCE | 90 | tr[d] | - | - |
| 4 | **A** | DMSO | 105 | tr[d] | - | - |
| 5 | **A** | $CH_3CN$ | 90 | tr[d] | - | - |
| 6 | **A**[b] | - | 105 | - | - | - |
| 7 | **B** | toluene | 105 | - | - | - |
| 8 | **C**-**I**/DIPEA[c] | toluene | 105 | - | - | - |

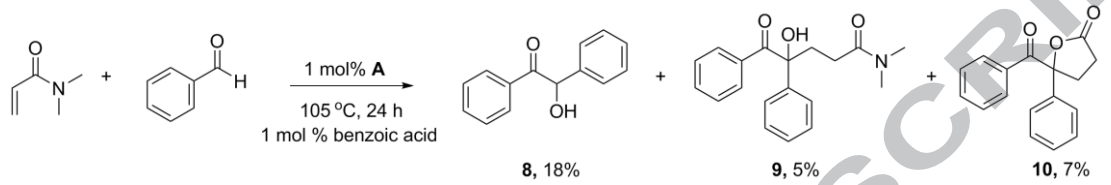
Dipp = 2,6-di-*iso*-propylphenyl, [a]calculated from $^1$H NMR spectrum, [b]1 mol % **A**, [c]1 mol% DIPEA, [d]trace, detected by GC.




**Scheme 4**. Proposed mechanism for the tail-to-tail dimerization and trimerization of DMAA, effected by NHC **A**.




**Scheme 5**. Homo- and cross-coupling of DMAA and MMA, catalyzed by NHC **A**.




**Scheme 6**. The reaction of benzaldehyde and DMAA catalyzed by NHC **A**.

*III. The NHC-catalyzed cross-coupling of DMAA and MMA*

The NHC-catalyzed cross-coupling of DMAA and MMA (1:1) was investigated under the conditions optimized for DMAA-oligomerization (Scheme 5). It was found that the tail-to-tail dimerization (**3**) and trimerization (**4**) products of DMAA were obtained in 26 and 7 % yield, whereas the mixed cross coupling products **5** and **6** were formed in 26 and 6 % yield. Additionally, 16 % of the MMA homodimer **7** were isolated (combined yield 81%).

*IV. The reaction of DMAA with benzaldehyde catalyzed by NHC **A***

The NHC-catalyzed reaction of DMAA with benzaldehyde (1:1) was performed as shown in Scheme 6. In the presence of 1 mol % of carbene **A** and 1 mol % of benzoic acid as co-catalyst, benzoin (**8**), the Michael addition product of benzoin to DMAA (**9**), and the lactone (**10**) were formed.[12] The molecular structure of the Michael product **9** was unambiguously proven by X-ray crystallography (Figure 1).[13] In the absence of the benzoic acid co-catalyst, no product formation was observed. As a control experiment, a mixture of preformed benzoin and DMAA was exposed to DBU. Again, the formation of the Michael addition products **9** and **10** was detected by GC-MS. From this result, we conclude that the NHC **A** promotes both benzoin formation from benzaldehyde (as Umpolung catalyst), and subsequent Michael addition of the latter to DMAA (as Brønsted base).

In conclusion, our studies on the first organocatalytic tail-to-tail oligomerization of DMAA gave the dimer **3** and the new trimer **4**. The reaction mechanism and the intermediates were proposed based on NMR and ESI-MS analyses. Furthermore, we report the first example of a NHC-catalyzed cross coupling of DMAA and MMA, and the reaction of benzaldehyde/benzoin with DMAA catalyzed by a NHC.

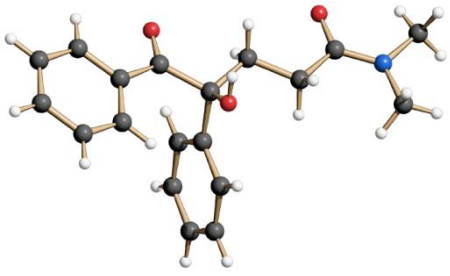


**Figure 1**. X-ray crystal structure of the alkylated benzoin **9**.

## Acknowledgments

This work was supported by the Thailand Research Fund *via* the Royal Golden Jubilee Ph.D. program, Khon Kaen University (0353/2551), and by BASF SE.

## References and notes

1. (a) Grossmann, A.; Enders, D. *Angew. Chem. Int. Ed.* **2012**, *51*, 314-325; *Angew. Chem.* **2012**, *124*, 320-332. (b) Douglas, J.; Churchill, G.; Smith, A. D. *Synthesis* **2012**, *44*, 2295-2309. (c) Mahatthananchai, J.; Bode, J. W. *Acc. Chem. Res.* **2014**, *47*, 696-707. (d) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511-3522. (e) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485-496. (f) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307-9387.
2. (a) Breslow, R. *J. Am. Chem. Soc.* **1957**, *79*, 1762-1763. (b) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719-3726.
3. Ukai,T.; Tanaka, R.; Dokawa, T. *J. Pharm. Soc. Jpn*. **1943**, *63*, 296-300.
4. (a) Stetter, H.; Kuhlmann, H. *Org. React*. **1991**, *40*, 407-496. (b) Stetter, H.; Schreckenberg, M. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 81.
5. Fischer, C.; Smith, S. W.; Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 1472-1473.
6. (a) Biju, A. T.; Padmanaban, M.; Wurz, N. E.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 8412-8415; *Angew. Chem.* **2011**, *123*, 8562-8565. (b) Schedler, M.; Wurz, N. E.; Daniliuc, C. G.; Glorius, F. *Org. Lett.* **2014**, *16*, 3134-3137.
7. (a) Matsuoka, S.; Ota, Y.; Washio, A.; Katada, A.; Ichioka, K.; Takagi, K.; Suzuki, M. *Org. Lett*. **2011**, *13*, 3722-3725. (b) Kato, T.; Ota, Y.; Matsuoka, S.; Takagi, K.; Suzuki, M. *J. Org. Chem.* **2013**, *78*, 8739-8747. (c) Kato, T.; Matsuoka, S.; Suzuki, M. *J. Org. Chem.* **2014**, *79*, 4484-4491.
8. Matsuoka, S.; Namera, S.; Washio, A.; Takagi, K.; Suzuki, M. *Org. Lett.* **2013**, *15*, 5916-5919.
9. Higashimura, M.; Imamura, K.; Yokogawa, Y.; Sakakibara, T. *Chem. Lett.* **2004**, *33*, 728-729.
10. (a) Berkessel, A.; Elfert, S.; Etzenbach-Effers, K.; Teles, J. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 7120-7124; *Angew. Chem.* **2010**, *122*, 7275-7279. (b) Berkessel, A.; Elfert, S.; Yatham, V. R.; Neudörfl, J.-M.; Schlörer, N. E.; Teles, J. H. *Angew. Chem. Int. Ed.* **2012**, *51*, 12370-12374; *Angew. Chem.* **2012**, *124*, 12537-12541. (c) Berkessel, A.; Yatham, V. R.; Elfert, S.; Neudörfl, J.-M. *Angew. Chem. Int. Ed.* **2013**, *52*, 11158-11162; *Angew. Chem.* **2013**, *125*, 11364-11369. (d)

Berkessel, A.; Elfert, S. *Adv. Synth. Catal.* **2014**, *356*, 571-578. (e) Yatham, V. R.;. Neudörfl, J.-M.; Schlörer, N. E.; Berkessel, A. *Chem. Sci*. **2015**, *6*, 3706-3711.

11. ESI-MS analysis of the crude reaction mixture also points to the formation of a DMAA tetramer [m/z = 419.3 ($+Na^+$)], see Supporting Information (Figure 74S).
12. Ye, W.; Cai, G.; Zhuang, Z.; Jia, X.; Zhai, H. *Org. Lett.* **2005**, *7*, 3769-3771.
13. CCDC 1406034 (**9**) contains supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/ cif.

Graphical abstract