Tetrahedron Letters 53 (2012) 863–867

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Amberlyst-15 mediated synthesis of 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones and their crystal structure analysis

P. VNS Murthy [a], D. Rambabu [a,b], G. Rama Krishna [c], C. Malla Reddy [c], K.R.S. Prasad [a], M.V. Basaveswara Rao [d], Manojit Pal [b,*]

[a] Department of Chemistry, K L University, Vaddeswaram, Guntur 522502, AP, India
[b] Institute of Life Sciences, University of Hyderabad Campus, Hyderabad 500 046, India
[c] Department of Chemical Sciences, Indian Institute of Science Education and Research, Kolkata, West Bengal 741252, India
[d] Department of chemistry, Krishna University, Machilipatnam 521001, AP, India

ARTICLE INFO

Article history:
Received 20 October 2011
Revised 1 December 2011
Accepted 7 December 2011
Available online 13 December 2011

Keywords:
2,3-Dihydroquinazolin-4(1*H*)-ones,
Aldehydes
Amberlyst-15

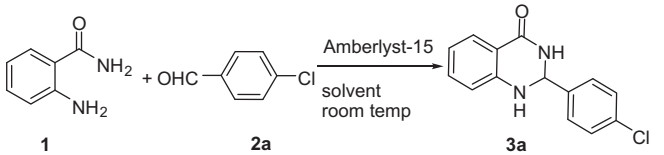
ABSTRACT

An efficient and clean method has been developed for the synthesis of 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones using Amberlyst-15 as a recyclable catalyst. A variety of dihydroquinazolinones were prepared from 2-aminobenzamide and aldehydes under mild conditions in excellent yields. Further structure elaboration of one compound and the crystal structure analysis and hydrogen bonding patterns of the two compounds prepared by using this methodology is presented.

2,3-Dihydroquinazolin-4(1*H*)-ones, an important class of heterocyclic compounds influence numerous cellular processes. This is exemplified by their broad range of pharmacological properties, for example, anticancer, antitumor, antibiotic, antidefibrillatory, antipyretic, analgesic, antihypertonic and diuretic activities.[1–11] They are also useful as antihistamine, antidepressant, and vasodilating agents. A number of synthetic methods have been reported to prepare this class of compounds in the past few years. These include the use of iridium,[12] citric acid,[13] [bmim]HSO_4,[14] iodine,[15] ammonium chloride,[16] gallium trifluoro methane sulfonate,[17] ionic liquids,[18] bronsted acids,[19] phosphoric acid,[20] copper chloride,[21] tetra butyl ammonium bromide,[22] and $TiCl_4$/Zn.[23] Many of these methods however, suffer from drawbacks, such as low yields of products, the requirement of longer reaction time and high temperature along with the use of non-recyclable catalysts. Moreover, preparation of required catalysts is cumbersome in some cases. Thus, development of a facile, atom-efficient, and eco-friendly method is highly desirable. In recent years, heterogeneous catalysis has played the central role in various organic transformations.[24] As an inexpensive and commercially available heterogeneous catalyst Amberlyst-15 attracted our attention[25a] due to its non-hazardous nature and easy removal from the reaction mixture, for example, via simple filtration. Due to our continuing interest in quinazolinone derivatives[25b] we now report an Amberlyst-15 mediated practical and efficient synthesis of 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones **3** from 2-aminobenzamide **1** and aldehyde **2** (Scheme 1).

In our initial study, 4-chlorobenzaldehyde (**2a**) was reacted with 2-aminobenzamide (**1**) in the presence of Amberlyst-15 in

Table 1
The reaction of **1** and **2a** in the presence of Amberlyst-15 under various conditions[a]



1 **2a** **3a**

Entry	Solvent	Time (min)	Yield[b] (%)
1	DCM	30	95
2	MeOH	30	92
3	Toluene	30	80
4	CH_3CN	10	98 (97, 96, 95)[c]
5	CH_3CN	60	30[d]
6	CH_3CN	60	70[e]

[a] Reaction and conditions: all the reactions were carried out using 2-aminobenzamide **1** (1.0 mmol), aldehyde **2a** (1.0 mmol) and Amberlyst-15 (10%, w/w) at room temperature.
[b] Isolated yield.
[c] Catalyst was reused for additional three runs and figures within parentheses indicate the corresponding yields for each run.
[d] The reaction was carried out without Amberlyst-15.
[e] The reaction was carried out without Amberlyst-15 under sonication.

* Corresponding author. Tel.: +91 40 6657 1500; fax: +91 40 6657 1581.
E-mail addresses: manojitpal@rediffmail.com, palmanojit@yahoo.co.uk (M. Pal).

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doi:10.1016/j.tetlet.2011.12.023

Table 2
Amberlyst-15 mediated synthesis of 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones[a]

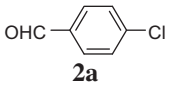
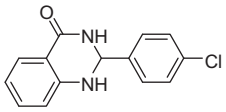
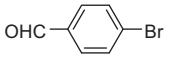
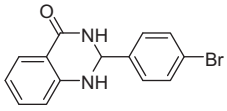
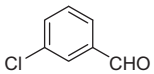
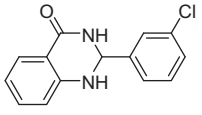
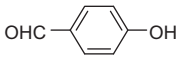
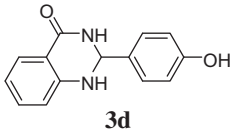
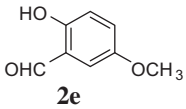
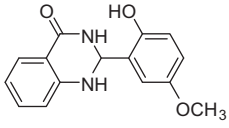
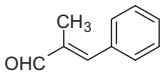
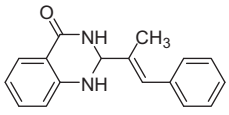
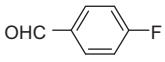
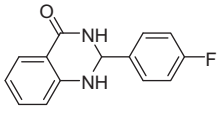
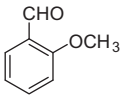
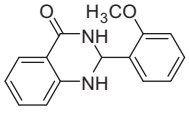
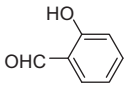
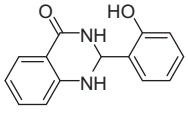
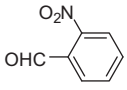
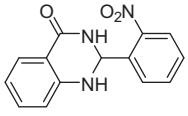
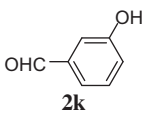
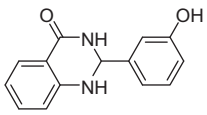
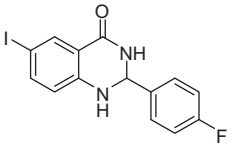
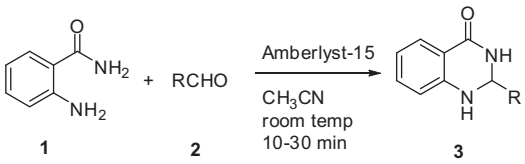
Entry	Aldehyde (**2**)	Product (**3**)	Time (min)	Yield[b] (%)
1	 **2a**	 **3a**	10	98
2	 **2b**	 **3b**	20	98
3	 **2c**	 **3c**	10	98
4	 **2d**	 **3d**	20	97
5	 **2e**	 **3e**	25	97
6	 **2f**	 **3f**	30	96
7	 **2g**	 **3g**	15	98
8	 **2h**	 **3h**	15	97
9	 **2i**	 **3i**	20	97
10	 **2j**	 **3j**	15	98
11	 **2k**	 **3k**	20	97

Table 2 (*continued*)

Entry	Aldehyde (**2**)	Product (**3**)	Time (min)	Yield[b] (%)
12	**2g**	 **3l**	30	96[c]

[a] Reaction and conditions: all the reactions were carried out using 2-aminobenzamide **1** (1.0 mmol), an appropriate aldehyde **2** (1.0 mmol) and Amberlyst-15 (10%, w/w) in CH_3CN at room temperature.
[b] Isolated yield.
[c] 2-Amino-5-iodobenzamide (**4**) was used in place of compound **1**.



Scheme 1. Amberlyst-15 mediated synthesis of 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones.

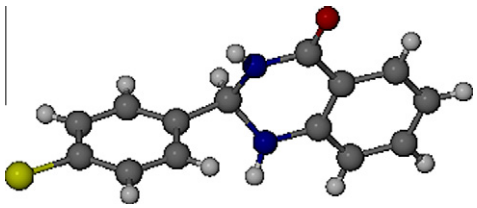


Figure 1. ORTEP representation of the compound **3a** (Thermal ellipsoids are drawn at 50% probability level).

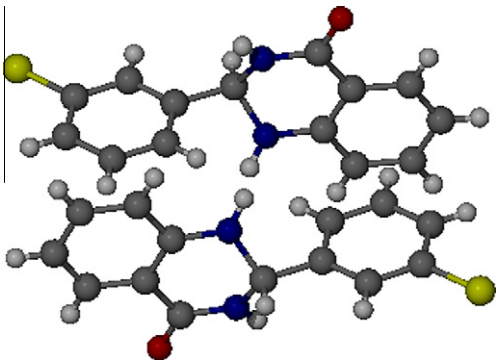
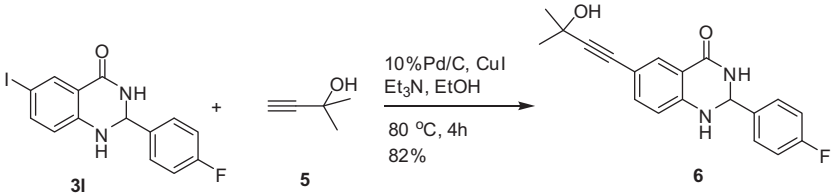


Figure 2. ORTEP representation of the compound **3c** (Thermal ellipsoids are drawn at 50% probability level).

dichloromethane (DCM) at room temperature for 30 min when the expected product **3a** was obtained in a 95% yield (Table 1, entry 1). The use of other solvents such as methanol and toluene was examined but did not improve the product yields (Table 1, entries 2 and 3). However, almost quantitative yields was achieved when the reaction was carried out in CH_3CN and completed within 10 min (Table 1, entry 4). The catalyst recovered from the reaction mixture was also tested for its recyclability at least for three times and the desired product was isolated in good yields in each run (Table 1, entry 4). To understand the role of Amberlyst-15 the reaction was performed in its absence when **3a** was isolated only in 30% yield after 60 min (Table 1, entry 5). The use of sonication increased the product yield but did not decrease the reaction time (Table 1, entry 6). Thus Amberlyst-15 was identified as an efficient and reusable catalyst for the present reaction.

This observation encouraged us to extend the scope and generality of this methodology. A variety of aryl aldehydes (**2**) therefore were reacted with 2-aminobenzamide (**1**) in the presence of Amberlyst-15 under the conditions[26] of entry 4 of Table 1 and the results are summarized in Table 2. The reaction proceeded smoothly in all these cases to give the corresponding 2,3-dihydroquinazolin-4(1*H*)-ones in excellent yields. Aldehydes containing various substituents such as electron donating F, Cl, Br, OH and OMe and electron withdrawing NO_2 were well tolerated and did not affect the product yields (Table 2, entries 1–5 and 7–11). The use of a cinnamaldehyde derivative also afforded the desired product in excellent yield (Table 2, entry 6).

The use of 2-amino-5-iodobenzamide (**4**) in place of **1** was successful (Table 2, entry 12) and the corresponding product, that is, the iodo derivative **3l** has potential for further structural elaboration via palladium catalyzed C–C or C–N bond forming reactions thereby introducing diversity into the quinazolinone ring. This is exemplified by alkynylation of compound **3l** under Pd/C–Cu catalysis[27] as shown in Scheme 2. All the 2,3-dihydroquinazolin-4(1*H*)-ones synthesized can easily be oxidized[21] to their quinazolin-4(3*H*)-one analogs that are known to possess pharmacological activities and be integral part of some natural products. It is worthy to mention that the present methodology does not require the use of microwave irradiation and therefore amenable for scale up preparation of compound **3**.



Scheme 2. Pd/C-mediated alkynylation of compound **3l**.

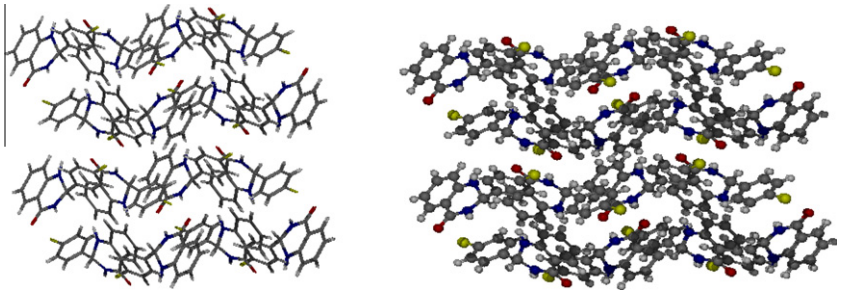


Figure 3. Showing the packing patterns in compound **3a**.

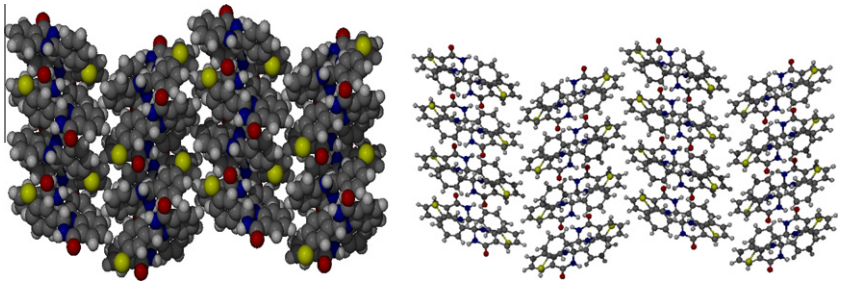


Figure 4. Showing the packing patterns in compound **3c**.

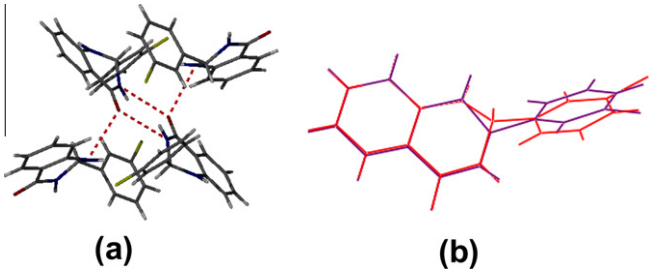


Figure 5. (a) Showing the hydrogen bonding patterns in two molecules of asymmetric unit in compound **3c**; (b) Showing the overlay diagram of compound **3c** conformer-a (Red), conformer-b (purple) color.

All the compounds synthesized were well characterized by spectral data (NMR, MS and IR). Additionally, the molecular structure of two representative compounds, for example, **3a** and **3c** was established unambiguously by single crystal X-ray diffraction (Figs. 1 and 2).[28,29] Further crystal structure analysis were carried out to understand the packing and/or hydrogen bonding patterns in crystals of these molecules and results are summarized in the following sections.

Compound **3a** crystallizes in Monoclinic P2 (1)/c space group with one molecule in the asymmetric unit (Z: 4 Z′: 0) (Fig. 3). Two *p*-chlorophenyl rings of the molecules in the asymmetric unit are not in coplanar with dihydroquinazolin-4-one of the two molecules. The torsion angles of the phenyl ring and dihydroquinazolin-4-one moieties are (C8–C9–C10–C11 175.4(2), C8–C9–C14–C13 176.5(2) and C7–N2–C8–C9 159.54(19), C8–N2–C7–O1 170.3(2). Here one molecule present in the asymmetric unit forms the dimer synthon with amide functional group present in dihydroquinazolin-4-one, and formed dimer synthon via O–H···N and weak Vander Waal Cl···Cl interactions. These interactions propagate 3D corrugated layered structure.

Compound **3c** crystallizes in Orthorhombic Pca2 (1) space group with two molecules in the asymmetric unit (Z: 8 Z′: 0) (Fig. 4).The two *m*-chlorophenyl rings of the molecules in the asymmetric unit are not in coplanar with dihydroquinazolin-4-one of the two molecules. The torsion angles of the phenyl ring and dihydroquinazolin-4-one moieties are (C8–C9–C10–C11 178.6(2), C8–C9–C14–C13 178.9(2) and C7–N2–C8–C9 162.6(2), C8–N2–C7–O1 163.9(2). The two molecules in the asymmetric unit form same hydrogen bonding patterns in the crystal structure. These molecules are conformationally different which were showed in Figure 5. Here two molecules have formed hydrogen bonding with amide as functional group present in dihydroquinazolin-4-one, and formed dimer synthon via O–H···N. These interactions propagate in 3D corrugated layered structure.

In conclusion, we have described Amberlyst-15 mediated practical and general synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones from 2-aminobenzamide and aldehydes under mild conditions. The notable advantages of this protocol include (i) simple operational procedure, (ii) the use of an inexpensive and heterogeneous thereby recyclable catalyst, (iii) shorter reaction time and (iv) high yields of products. The crystal structure analysis and hydrogen bonding patterns of two compounds prepared by using this methodology are presented. We believe that this methodology would find wide usage in the preparation of dihydroquinazolinone based library of small molecules useful not only for medicinal chemistry/drug discovery but also for studying their solid state properties.

Acknowledgment

The authors sincerely thank the management of Institute of Life Sciences for continuous support and encouragement.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.023.

References and notes

1. Yale, H. L.; Kalkstein, M. *J. Med. Chem.* **1967**, *10*, 334.
2. Neil, G. L.; Li, L. H.; Buskirk, H. H.; Moxlcy, T. E. *Cancer Chemother.* **1972**, *56*, 163.
3. Bonola, G.; Da Re, P.; Magistretti, M. J.; Massarani, E.; Setnikar, I. *J. Med. Chem.* **1968**, *11*, 1136.

4. Bolger, J. W. US patent application US3257397A, Jun 21, 1966; *Chem. Abstr.* **1966**, *66*, 8933b.
5. Boehringer Sohn, C. H. French Patent M 2588, 1964; *Chem. Abstr.* **1964**, *61*, 16075h.
6. Alaimo, R. J.; Russel, H. E. *J. Med. Chem.* **1972**, *15*, 335.
7. Cohen, E.; Klarberg, B.; Vaughan, J. R. *J. Am. Chem. Soc.* **1959**, *81*, 5508.
8. Okumura, K.; Oine, T.; Yamada, Y.; Hayashi, G.; Nakama, M. *J. Med. Chem.* **1968**, *11*, 348.
9. Instituto De Angeli S. P. A. French Patent M 1893, 1964; *Chem. Abstr.* **1964**, 60, 3956.
10. Levin, I.; Chan, P. S.; Bailey, T.; Katocs, A. S.; Venkatesan, A. M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1141.
11. Chinigo, G. M.; Paige, M.; Grindrod, S.; Hamel, E.; Dakshanamurthy, S.; Chruszcz, M.; Minor, W.; Brown, M. L. *J. Med. Chem.* **2008**, *51*, 4620.
12. Jianguang, Z.; Jie, F. *J. Org. Chem*. **2011** dx. doi: org/10.1021/jo201054k.
13. Ghorbani-Choghamarani, A.; Taghipour, T. *Lett. Org. Chem.* **2011**, *8*, 470.
14. Darvatkar, N. B.; Bhilare, S. V.; Deorukhkar, A. R.; Raut, D. G.; Salunkhe, M. M. *Green Chem. Lett. Rev*. **2010**, *3*, 301.
15. Zeng, L.-Y.; Cai, C. *J. Heterocycl. Chem.* **2010**, *47*, 1035.
16. Shaabani, A.; Maleki, A.; Mofakham, H. *Synth. Commun.* **2008**, *38*, 3751.
17. Chen, J.; Wu, D.; He, F.; Liu, M.; Wu, H.; Ding, J.; Su, W. *Tetrahedron Lett.* **2008**, *49*, 3814.
18. Chen, J. X.; Su, W. K.; Wu, H. Y.; Liu, M. C.; Jin, C. *Green Chem.* **2007**, *9*, 972.
19. Rueping, M.; Antonchick, A. P.; Sugiono, E.; Grenader, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 908.
20. Cheng, X.; Vellalath, S. K.; Goddard, R.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 15786.
21. Abdel-Jalil, R. J.; Voelter, W.; Saeed, M. *Tetrahedron Lett.* **2004**, *45*, 3475.
22. Davoodnia, A.; Allameh, S.; Fakhari, A. R.; Tavakoli-Hoseini, N. *Chinese Chem. Lett.* **2010**, *21*, 550.
23. Shi, D. Q.; Rong, L. C.; Wang, J. X.; Zhuang, Q. Y.; Wang, X. S.; Hu, H. W. *Tetrahedron Lett.* **2003**, *44*, 3199.
24. (a) Lee, S. H.; Park, D. R.; Kim, H.; Lee, J.; Jung, J. C.; Woo, S. Y.; Song, W. S.; Kwon, M. S.; Song, I. K. *Catal. Commun.* **2008**, *9*, 1920; (b) Park, S.; Cho, K. M.; Youn, M. H.; Seo, J. G.; Baeck, S. H.; Kim, T. J.; Chung, Y. M.; Oh, S. H.; Song, I. K. *Catal. Lett.* **2008**, *122*, 349; (c) Song, I. K.; Lee, W. Y. *Appl. Catal. A: Gen.* **2003**, *256*, 77.
25. (a) Kumar, S. K.; Iqbal, J.; Pal, M. *Tetrahedron Lett.* **2009**, *50*, 6244; (b) Kumar, K. S.; Kumar, P. M.; Reddy, M. A.; Ferozuddin, M.; Sreenivasulu, M.; Jafar, A. A.; Krishna, G. R.; Reddy, C. M.; Rambabu, D.; Kumar, K. S.; Pal, S.; Pal, M. *Chem. Commun.* **2011**, *47*, 10263.
26. General procedure for the preparation of compound **3**: A mixture of 2-aminobenzamide **1** or **4** (1.0 mmol), aldehyde **2** (1.0 mmol) and Amberlyst-15 (10%, w/w) in acetonitrile (5 mL) was stirred at room temperature for the time indicated in Table 2. After completion of the reaction (indicated by TLC) the solid separated was filtered, washed by diethyl ether (2×5 mL), dried and treated with EtOAc (15 mL). After stirring for 10 min the mixture was filtered to remove the insoluble catalyst. The filtrate was collected and concentrated under vacuum. The solid isolated was triturated in diethyl ether, filtered and dried to give the desired product.
27. Pal, M. *Synlett* **2009**, 2896.
28. Crystal data of **3a**: Molecular formula = $C_{14}H_{11}ClN_2O$, Formula weight = 258.21, Crystal system = Monoclinic, space group = *P*2(1)/c, a = 12.9334(9) Å, b = 8.9167(6) Å, c = 11.2545(7) Å, V = 1237.07(14) Å^3, T = 296(2) K, Z = 4, D_c = 1.405 Mg m^{-3}, μ(Mo-K_α) = 0.30 mm^{-1}, 1974 reflections measured, 2578 independent reflections, 1986 observed reflections [$I > 2.0\ \sigma\ (I)$], R_1_obs = 0.050, Goodness of fit = 1.079. Crystallographic data (excluding structure factors) for **3a** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 848113.
29. Crystal data of **3c**: Molecular formula = $C_{14}H_{11}ClN_2O$, Formula weight = 258.21, Crystal system = Orthorhombic, space group = *P*ca2(1), a = 10.9794(6) Å, b = 9.1619(6) Å, c = 23.5375(16) Å, V = 2367.7(18) Å^3, T = 296(2) K, Z = 8, D_c = 1.488 Mg m^{-3}, μ(Mo-K_α) = 0.31 mm^{-1}, 1440 reflections measured, 3816 independent reflections, 3522 observed reflections [$I > 2.0\ \sigma\ (I)$], R_1_obs = 0.028, Goodness of fit = 1.028. Crystallographic data (excluding structure factors) for **3c** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 848112.