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Dehydrative intramolecular nitrone cycloaddition in confined aqueous media: a green chemical route to *cis*-fused chromano[4,3-*c*]isoxazoles

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ABSTRACT

An efficient synthetic route to the formation of *cis*-fused chromano[4,3-*c*]isoxazoles via dehydrative intramolecular 1,3-dipolar nitrone cycloaddition in organized aqueous media in the presence of a surfactant (viz. CTAB) as catalyst was developed, which indeed appeared to be green and a more sustainable method than the existing methods with the additional advantage of easy isolation of products.

Although nature uses aqueous environment in most of its chemical transformations, water as solvent was totally neglected in organic reactions/syntheses till the end of the last century mostly due to poor solubility of organic compounds. However, most of the organic solvents and reagents are not environment benign substances, which is now a pronounced environmental concern. The concept of 'green chemistry'[1] and its 12 principles[2] have emerged as a major solution to this problem with ways to develop clean and more sustainable chemical processes. From this point of view water is the solvent of choice for synthetic purposes[3] because it is environment friendly, cheap, non-toxic, non-flammable, widely abundant in nature, and also provides easy synthetic approaches, for example, no need for vigorous drying of the solvents or maintaining tricky anhydrous reaction systems, and scope of easy isolation of products. In addition, water has unique physical and chemical properties, which sometimes lead to reactivity or selectivity that cannot be attained in organic medium.[3g,4] The problem of insolubility and hydrolytic decomposition of many organic compounds in water may be solved by the use of surfactants, which form a colloidal, micellar or other organized phase that serves as nanoreactors in aqueous media.[5] The confined hydrophobic interior of the nanoreactor not only solubilizes the organic reagents but also brings them in close proximity and in the process enhances the efficiency as well as the rate of a chemical reaction. These nanoreactors have been proven as a useful tool to carry out various types of catalytic reactions in water.[3d–f,5,6] In particular, dehydration reactions, which otherwise need anhydrous conditions and thus one of the most challenging tasks to accomplish in water, have been successfully carried out by our group[7] and others[8] in the confined nanoreactor systems under aqueous environment.

1,3-Dipolar nitrone cycloaddition is one of the most useful ways for the construction of a variety of nitrogen-containing five-membered heterocycles, some of which are biologically and pharmaceutically important compounds.[9] In particular, intramolecular nitrone-olefin cycloadditions have been utilized to obtain structurally more complex bi- or tri-cyclic isoxazolidines of either biological significance or as useful synthetic intermediates for target molecules.[10] Particularly, certain fused isoxazoline/isoxazole with chromano moiety are known to possess antidepressant, antipsychotic and antianxiolytic activities.[11] The labile nature of N–O bond of chromano-isoxazoles has also been exploited by several groups of researchers and used as synthetic precursors for the construction of pharmaceutically important amino alcohols.[12] In spite of their bioactivity and potential pharmacological utility not many methods have been developed for chromano-isoxazoles.[12a–c,13] Moreover, existing methods are based on conventional synthetic protocols involving use of hazardous reagents, toxic solvents or relatively harsh reaction conditions.[12a–c,13] These facts prompted us to develop a better, environment friendly alternative. As per our current efforts on the development of safe and 'green' protocols for organic reactions in aqueous media, we have reported one-pot processes for nitrone formation followed by its intermolecular cycloaddition to form various heterocyclic compounds.[7a] Herein, we report an environment friendly synthetic route to chroma-

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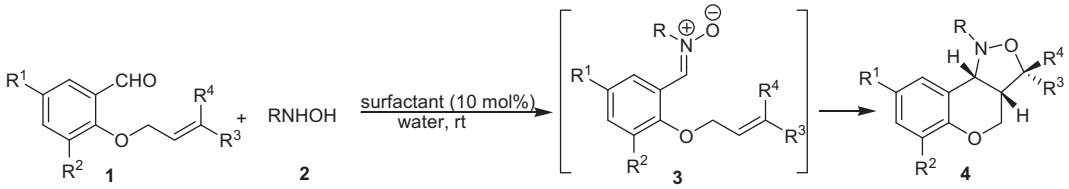

Scheme 1. Synthesis of *cis*-fused chromano[4,3-*c*]isoxazoles in confined aqueous media.

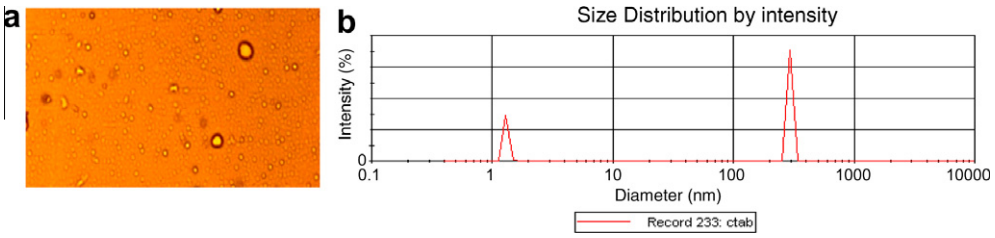

Figure 1. (a) A typical optical micrograph of nanoreactors formed in an aqueous solution of CTAB, *O*-allyl salicylaldehyde and phenyl hydroxylamine. (b) DLS data of CTAB.

no[4,3-*c*]isoxazoles via intramolecular 1,3-dipolar cycloaddition by in situ formation of nitrones derived from *O*-allyloxy salicylaldehydes in organized aqueous media (Scheme 1).

At the beginning of our study, we focused our attention on optimizing the reaction conditions. In this direction, the formation of the emulsion droplets, so called nanoreactors were confirmed by taking an optical micrograph of a different surfactant containing aqueous solutions of reactants before the reaction would actually proceed (Fig. 1a). Dynamic light scattering (DLS) experiments of those solutions revealed that the corresponding size of emulsion droplets is in nanometre range (Fig. 1b).

To find out if a suitable surfactant that would act as a catalyst for the cycloaddition reaction, a model reaction was carried out between *O*-allyl salicylaldehyde (**1a**) and phenyl hydroxylamine (**2a**) using various surfactants as catalysts (Table 1). Although polyethylene oxide based surfactants afforded the desired product in moderate yield after 48 h, reaction was much faster and high yielding in the presence of anionic surfactants. However, acidic surfactant, dodecylbenzene sulfonic acid (DBSA) was not useful in this reaction (entry 8, Table 1). Among all the surfactants cetyl trimethylammonium bromide (CTAB) was found to be most obvious choice for further exploration of the methodology with other *O*-allyl salicylaldehyde derivatives. In our next study, the role of the surfactant as well as the nanoreactor was established by carrying out the same reaction in the presence of organic co-solvents (Table 2). Although organic solvents ensure solubility of organic components in water, only trace amount of product was obtained in the absence of surfactant (viz. CTAB) after several hours. More importantly, the presence of surfactant could not boost the product formation; the reactions were very sluggish in different co-solvents. This fact signifies the role of nanoreactor as well since it drives the dehydration step forward by expelling the product water molecule out of its hydrophobic interior and consequently, shifting the equilibrium towards the product side (Fig. 2). On the contrary, the presence of co-solvent would presumably have taken the reactants out of hydrophobic emulsion droplets into the solution phase slowing down the rate of the dehydration reaction.

To study intramolecular cycloaddition reaction on various substrates, phenolic –OH group of salicylaldehyde and its selective derivatives were first alkylated with an allyl group or its homologues adopting standard procedure. Next, *O*-allyl derivatives

Table 1
Study on catalytic activity of different surfactants in cycloaddition reaction

Entry	Surfactant[a]	Time (h)	Yield of **4a** (%)
1.	CTAB	9	92
2.	SDS	18	82
3.	SBDS	20	80
4.	Triton X-100	48	56
5.	Tween 20	48	58
6.	Tween 80	48	55
7.	Triton CF 10	48	60
8.	DBSA	48	No pdt

[a] The reaction was carried out between 0.5 mmol of *O*-allyl salicylaldehyde (**1a**) and 0.52 mmol of phenyl hydroxylamine (**2a**) in presence of 0.05 mmol of surfactants in 2 mL of water.

Table 2
Effect of co-solvents in cycloaddition reaction

Entry	**A**[a]	Time (h)	Yield of **4a** (%)
1.	—	>48	No rxn.
2.	10% v/v MeOH	>48	8
3.	10% v/v MeOH + 10 mol% CTAB	>48	28
4.	15% v/v CH_3CN	>48	10
5.	15% v/v CH_3CN + 10 mol% CTAB	>48	22
6.	10% v/v THF	>48	<5
7.	10 mol% CTAB	9	92

[a] An aqueous solution of 0.5 mmol of *O*-allyl salicylaldehyde (**1a**) and 0.52 mmol of phenyl hydroxylamine (**2a**) was treated with **A** and the product was isolated after the said time.

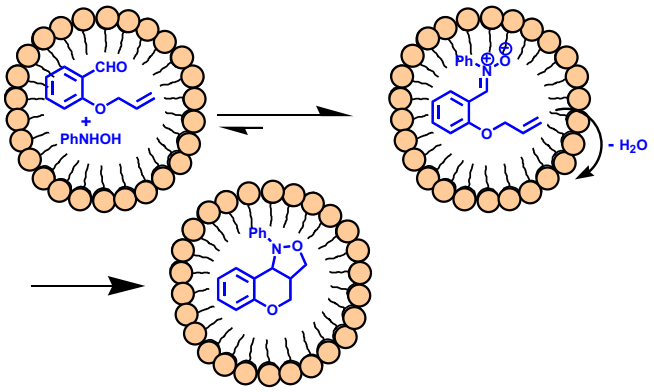

Figure 2. Nanoreactor promoted synthesis of chromano[4,3-*c*]isoxazole.

Table 3
Studies on intramolecular nitrone cycloaddition (refer to Scheme 1) with CTAB as catalyst

Entry	Salicylaldehyde derivative (**1**)	RNHOH	Product (**4**)	Time (h)	Yield (%)
1.	**1a**: $R^1 = R^2 = R^3 = R^4 = H$	Ph	**4a**	9	92
2.	**1b**: $R^1 = R^2 = R^3 = H$, $R^4 = CH_3$	Ph	**4b**	14	86
3.	**1c**: $R^1 = R^2 = H$, $R^3 = R^4 = CH_3$	Ph	**4c**[a]	20	85
4.	**1d**: $R^1 = Br$, $R^2 = R^3 = R^4 = H$	Ph	**4d**	12	88
5.	**1e**: $R^1 = Br$, $R^2 = H$, $R^3 = R^4 = CH_3$	Ph	**4e**[a]	22	84
6.	**1f**: $R^2 = OMe$, $R^1 = R^3 = R^4 = H$	Ph	**4f**	11	91
7.	**1g**: $R^2 = OMe$, $R^1 = H$, $R^3 = R^4 = CH_3$	Ph	**4g**[a]	22	85
8.	**1h**: $R^1 = NO_2$, $R^2 = R^3 = R^4 = H$	Ph	**4h**	9	88
9.	**1i**: $R^1 = NO_2$, $R^2 = H$, $R^3 = R^4 = CH_3$	Ph	**4i**[a]	21	86
10.	**1a**	$PhCH_2$	**4j**	11	94
11.	**1b**	$PhCH_2$	**4k**	15	89
12.	**1c**	$PhCH_2$	**4l**[a]	24	79
13.	**1d**	$PhCH_2$	**4m**	12	82
14.	**1f**	$PhCH_2$	**4n**	12	88
15.	**1h**	$PhCH_2$	**4o**	11	86

[a] Reported elsewhere; see Ref. 13a.

of salicylaldehyde (**1a–i**) were treated with N-substituted hydroxylamine in an aqueous medium in the presence of 10 mol % CTAB to afford corresponding nitrones, which undergo in situ stereoselective intramolecular cycloaddition to produce *cis*-fused 1-aryl-1,3a,4,9b-tetrahydro-3*H*-chromano[4,3-*c*]isoxazoles (**4a–o**) as the only isolated product in excellent yields (Table 3). It is worthy to note that after the reaction was over the products were isolated by cooling the reaction mixture at 5 °C for several hours and then by filtering off the crude product.[14] The sufficiently pure crude products were further purified by recrystallization. Although the current method competes equally in terms of yield and stereoselectivity, a combination of clean reaction profile and easy isolation of the product has a sheer advantage over the other available conventional methods.[12a–c,13] Noticeably, substituents in the aromatic ring of the *O*-allyl salicylaldehyde derivatives did not show any significant effect in the yield of chromano[4,3-*c*]isoxazoles (entry 4–9 and 11–13, Table 3), whereas, doubly substituted allyl moiety (i.e., prenyl group) although it did not reduce the yield but slowed down the reaction due to steric reason (entry 3, 5, 7, 9, 12, Table 3). The expected *cis* stereochemistry[13] of chromano[4,3-*c*]isoxazoles was initially determined by 2D NMR studies (COSY and NOESY). For example, **4c** showed the presence of a NOESY cross peak between H_2 and H_3 protons and a coupling constant (J_{H2-H3}) of 6.6 Hz, which clearly indicates that the five- and six-membered rings are *cis*-fused (Fig. 3).[13a] The six-membered ring presumably adopts a twisted structure,[13a] consistent with the observed coupling constant values $J_{H1'-H2} = 4.8$ Hz and $J_{H1-H2} = 9.8$ Hz. The presence of NOESY cross peaks between H_1–CH_3 (6′), H'_1–CH_3 (6′), H_3–CH_3 (6) and H_2–CH_3 (6) as well as NOESY cross peaks between H_A of the phenyl and H_a of the *N*-phenyl with CH_3 (6) further indicated the twisted structure of the six-membered ring of **4c**. The H_2 and H_3 coupling constant values of the other compounds are also in accordance with *cis* stereochemistry. The actual structure of these

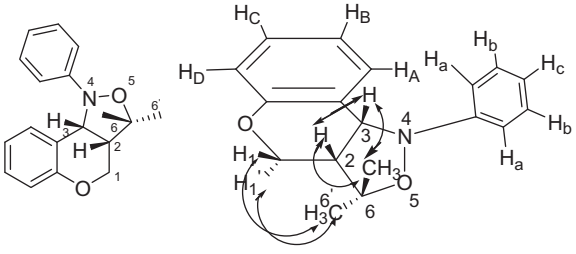

Figure 3. nOe interaction between the protons of **4c**.

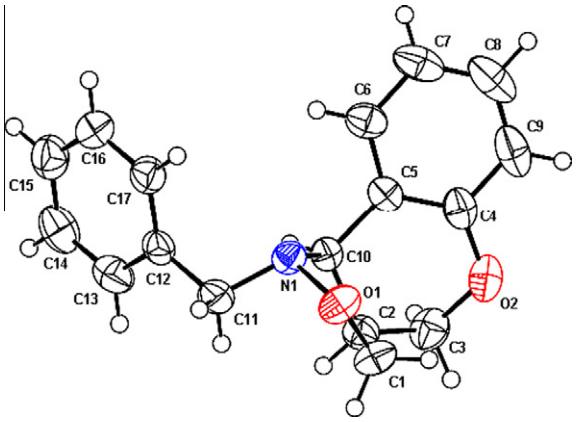

Figure 4. ORTEP diagram of **4j**.

molecules was reconfirmed by determining the X-ray crystal structure of a representative compound, **4j** (Fig. 4).

In conclusion, we have demonstrated a useful and 'green' method for the preparation of *cis*-fused chromano[4,3-*c*]isoxazoles via dehydrative intramolecular nitrone cycloaddition reaction in organized aqueous media. The method is more advantageous over existing methods due to a clean reaction profile, high yield, use of safe chemicals and easy isolation of the products.

Supplementary data

Crystallographic data (excluding structure factor) for the structure of **4j** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 784802. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.111.

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References and notes

1. (a) Anastas, P.; Heine, L. G.; Williamson, T. C. *Green Chemical Syntheses and Processes*; Oxford University Press: New York, 2000; (b) Lancaster, M. *Green Chemistry: An Introductory Text*; Royal Society of Chemistry: Cambridge, UK, 2002.; (c) Andraos, J. *Org. Process Res. Dev.* **2005**, *9*, 149.

2. (a) Hjeresen, D. L.; Kirchhoff, M. M.; Lankey, R. L. *Corporate Environ. Strategy* **2002**, *9*, 259; (b) Warner, J. C.; Cannon, A. S.; Dye, K. M. *Environ. Impact Assess. Rev.* **2004**, *24*, 775; (c) Sheldon, R. A. *Green Chem.* **2005**, *7*, 267.
3. (a) Lindström, U. M. *Organic Reactions in Water: Principles, Strategies and Applications*; Oxford, 2007.; (b) Grieco, P. A. *Organic Synthesis in Water*; Blackie: Academic & Professional, London, 1998; (c) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997. p 7950; (d) Herreríes, C. I.; Yao, X.; Li, Z.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546; (e) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68; (f) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095; (g) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159.
4. (a) Engberts, J. B. F. N.; Blandamer, M. J. *Chem. Commun.* **2001**, 1701; (b) Pirrung, M. C.; Sarma, K. D.; Wang, J. *J. Org. Chem.* **2008**, *73*, 8723.
5. (a) Lee, M.; Jang, C.-J.; Ryu, J.-H. *J. Am. Chem. Soc.* **2004**, *126*, 8082; (b) Vriezema, D. M.; Aragones, M. C.; Elemans, J. A. A. W.; Cornelissen, J. J. L. M.; Rowan, A. E.; Nolte, R. J. M. *Chem. Rev.* **2005**, *105*, 1445.
6. For recent examples see: (a) Cavarzan, A.; Scarso, A.; Strukul, G. *Green Chem.* **2010**, *12*, 790; (b) Hota, S. K.; Chatterjee, A.; Bhattacharya, P. K.; Chattopadhyay, P. *Green Chem.* **2009**, *11*, 169; (c) Akiyama, R.; Kobayashi, S. *Chem. Rev.* **2009**, *109*, 594; (d) Pandit, P.; Chatterjee, N.; Halder, S.; Hota, S. K.; Patra, A.; Maiti, D. K. *J. Org. Chem.* **2009**, *74*, 2581; (e) Bianchini, G.; Cavarzan, A.; Scarso, A.; Strukul, G. *Green Chem.* **2009**, *11*, 1517; (f) Sharma, S. D.; Gogoi, P.; Konwar, D. *Green Chem.* **2007**, *9*, 153; (g) Saito, A.; Numaguch, J.; Hanzawa, Y. *Tetrahedron Lett.* **2007**, *48*, 835; (h) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Mi, X.; Zheng, X.; Cheng, J.-P. *Tetrahedron* **2007**, *46*, 11307; (i) Das Sharma, S.; Gogoia, P.; Boruaha, M.; Konwar, D. *Synth. Commun.* **2007**, *37*, 2473.
7. (a) Chatterjee, A.; Maiti, D. K.; Bhattacharya, P. K. *Org. Lett.* **2003**, *5*, 3967; (b) Chatterjee, A.; Bhattacharya, P. K. *J. Org. Chem.* **2006**, *71*, 345.
8. (a) Manabe, K.; Iimura, S.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 11971; (b) Shirakawa, S.; Kobayashi, S. *Org. Lett.* **2007**, *9*, 311; (c) Kumar, A.; Gupta, M. K.; Kumar, M. *Tetrahedron Lett.* **2010**, *51*, 1582; (d) McKay, C. S.; Kennedy, D. C.; Pezacki, J. P. *Tetrahedron Lett.* **2009**, *50*, 1893.
9. (a) Padwa, A.; Pearson, W. H. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Wiley: New York, 2003. Chapter 1; (b) Revuelta, J.; Cicchi, S.; Goti, A.; Brandi, A. *Synthesis* **2007**, 485; (c) Broggini, G.; Zecchi, G. *Synthesis* **1999**, 905; (d) Frederickson, M. *Tetrahedron* **1997**, *53*, 403; (e) Piperno, A.; Giofre, S. V.; Iannazzo, D.; Romeo, R.; Romeo, G.; Chiacchio, U.; Rescifina, A.; Piotrowska, D. G. *J. Org. Chem.* **2010**, *75*, 2798; (f) Chiacchio, U.; Balestrieri, E.; Macchi, B.; Iannazzo, D.; Piperno, A.; Rescifina, A.; Romeo, R.; Saglimbeni, M.; Sciortino, T.; Vincenza, V.; Mastino, A.; Romeo, G. *J. Org. Chem.* **2005**, *48*, 1389; (g) Rescifina, A.; Chiacchio, M. A.; Corsaro, A.; Clercq, E. D.; Iannazzo, D.; Mastino, A.; Piperno, A.; Romeo, G.; Romeo, R.; Valveri, V. *J. Med. Chem.* **2006**, *49*, 709; (h) Chiacchio, U.; Iannazzo, D.; Piperno, A.; Romeo, R.; Romeo, G.; Rescifina, A.; Saglimbeni, M. *Bioorg. Med. Chem.* **2006**, *14*, 955; (i) Sadashiva, M. P.; Mallesha, H.; Hitesh, N. A.; Rangappa, K. S. *Bioorg. Med. Chem.* **2004**, *12*, 6389.
10. (a) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247; (b) Jeong, J. H.; Weinreb, S. M. *Org. Lett.* **2006**, *8*, 2309; (c) Tamura, O.; Iyama, N.; Ishibashi, H. *J. Org. Chem.* **2004**, *69*, 1475; (d) Dhavale, D. D.; Jachak, S. M.; Karche, N. P.; Trombini, C. *Tetrahedron* **2004**, *60*, 3009; (e) White, J. D.; Hansen, J. D. *J. Am. Chem. Soc.* **2002**, *124*, 4950; (f) Gribble, G. W.; Barden, T. C. *J. Org. Chem.* **1985**, *50*, 5900.
11. (a) Andres-Gil, J. I.; Bartolome-Nebreda, J. M.; Alcazar-Vaca, M. J.; Gracia-Martin, M. d. l. M.; Megens, A. A. H. P. U.S. Patent 113988, 2008.; (b) Andŕes, J. I.; Alćazar, J.; Alonso, J. M.; Alvarez, R. M.; Bakker, M. H.; Biesmans, I.; Cid, J. M.; Lucas, A. I. D.; Drinkenburg, W.; Ferńandez, J.; Font, L. M.; Iturrino, L.; Langlois, X.; Lenaerts, I.; Martŕnez, S.; Megens, A. A.; Pastor, J.; Pullan, S.; Steckler, T. *Bioorg. Med. Chem.* **2007**, *15*, 3649; (c) Pastor, J.; Alćazar, J.; Alvarez, R. M.; Andŕes, J. I.; Cid, J. M.; Lucas, A. I. D.; Díaz, A.; Ferńandez, J.; Font, L. M.; Iturrino, L.; Lafuente, C.; Martı'nez, S.; Bakker, M. H.; Biesmans, I.; Heylen, L. I.; Megens, A. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2917.
12. (a) Zhao, Q.; Han, F.; Romero, D. L. *J. Org. Chem.* **2002**, *67*, 3317; (b) Broggini, G.; Bruché, L.; Cappelletti, E.; Zecchi, G. *J. Chem. Research (S)* **1997**, 36; (c) Broggini, G.; Folcio, F.; Sardone, N.; Sonzogni, M.; Zecchi, G. *Tetrahedron: Asymmetry* **1996**, *7*, 797; (d) Kella-Bennani, A. E.; Soufiaoui, M.; Kerbal, A.; Fkih-Tetouaniz, S.; Bitit, N. *Tetrahedron* **1995**, *51*, 10923.
13. (a) Yadav, J. S.; Reddy, B. V. S.; Narsimhaswamy, D.; Narsimulub, K.; Kunwarb, A. C. *Tetrahedron Lett.* **2003**, *44*, 3697; (b) Baldoli, C.; Del Buttero, P.; Licandro, E.; Maiorana, S.; Papagni, A. *Tetrahedron: Asymmetry* **1995**, *6*, 1711; (c) Aftab, T.; Grigg, R.; Ladlow, M.; Sridharan, V.; Thornton-Pett, M. *Chem. Commun.* **2002**, 1754; (d) Abiko, A. *Chem. Lett.* **1995**, 357.
14. **General procedure for the syntheses of chromeno[4,3-*c*]isoxazoles**: To a solution of surfactant (0.05 mmol) in H_2O (2 mL) were added an *O*-allyl derivative of salicylaldehyde (0.5 mmol) and hydroxylamine (0.52 mmol, 1.05 equiv) successively at room temperature. The reaction was sonicated for 5 min and then stirred at room temperature for several hrs (see Table 3). The reaction mixture was then refrigerated at 5 °C overnight. The solid separated was filtered off and subsequently washed with distiled water (3×10 mL), dried and desiccated. The sufficiently pure crude product was recrystallized from a mixture of ethyl acetate and petrolium spirit (30:70).