Graphical Abstract

An environmentally benign approach for the synthesis of 3, 4, 5-trisubstituted 2-aminofurans under solvent-free conditions *via* isocyanide-based multicomponent approach

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An environmentally benign approach for the synthesis of 3, 4, 5-trisubstituted 2-aminofurans under solvent-free conditions *via* isocyanide-based multicomponent approach

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ABSTRACT

An efficient solvent-free procedure for the synthesis of 3, 4, 5-trisubstituted 2-aminofurans has been developed via a multicomponent strategy by the solid state condensation of finely grounded dibenzoylacetylene and aromatic aldehydes in presence of isocyanides at room temperature. Clean reaction profile, easy work-up procedure, non-chromatographic purification technique, short reaction times, high yields and solvent-free reaction conditions are the remarkable advantages of this procedure. Single crystal X-ray diffraction has been established for four structures.

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Multicomponent reactions (MCRs) are at a premium for the procurement of high levels of brevity and diversity, as they allow more than two building blocks to be combined in a practical and time saving one-pot operations.¹ By virtue of their convergence, productivity, facile execution and generally high yields of products, they have attracted much attention from the vantage point of combinatorial chemistry² and hence are perfectly suited for automated synthesis. Of utmost important in this area are the isocyanide-based MCRs such as the versatile Ugi and Passerini reactions.³ Among MCRs, Solvent-free ones⁴ for reasons of economy and pollution prevention have aroused the attention of organic and medicinal chemists and has expanded tremendously in the last decade to modernize classical procedures by making them safer, cleaner and easier to perform.⁵ Since the solvent-free conditions often reduce the E factor⁶ of reactions and their impact on the environment, it is probably the most efficient way to improve the 'greenness' of complex organic molecule syntheses⁷. As the solvent is generally the main source of waste, it is often claimed that the best solvent is no solvent⁸.

Furans are an important class of five membered O-heterocycles frequently present in biologically active compounds including natural products and pharmaceutical substances⁹. Of pivotal importance among the derivatives of furans are 2-aminofurans that serve as versatile synthetic intermediates in the synthesis of various useful compounds including aniline derivatives¹⁰, cyclohexanones¹¹, pyrroles¹² and maleic anhydrides.¹³ Importantly, Padwa reported that 2-aminofuran derivatives can undergo Diels-Alder reaction with activated dienophiles to form substituted anilines¹⁴ and indoles.¹⁵ Despite of diverse utility, their use is somehow

hampered by the limited availability of synthetic methods and such a limitation exists particularly for 3, 4, 5-trisubstituted 2-aminofurans. Hitherto methods for the preparation of 3, 4, 5-trisubstituted 2-aminofurans rely on reaction between α -bromoacetophenones and melonitrile,¹⁶ a cascade Stetter- γ -keto nitrile cyclisation reaction of aromatic aldehydes and acyldienemalonitriles¹⁷, and by nucleophilic addition of isocyanides to dimethyl acetylenedicarboxylate in the presence of mainly aldehydes,¹⁸ acids¹⁹ or acyl chlorides.²⁰ Recently, regioselective synthesis of 3, 4, 5-trisubstituted 2-aminofurans *via* a multicomponent reaction strategy has been carried out in which 3 and 4 positions are functionalized with ester and keto groups²² respectively. However, limitation of these methods involve either laborious/tedious procedures or high temperature conditions or use of toxic solvents while as some are specific to given substituent pattern. Despite the previous accomplishments to obtain 3, 4, 5-trisubstituted 2-aminofuran scaffolds, an economical and ecofriendly route under solvent-free conditions is still required.

Dibenzoylacetylene (DBA) is an extremely versatile tool for organic synthesis, is a powerful Michael acceptor, and can take up various nucleophiles. Using it in an initial reaction as a Michael acceptor and then carrying out a cyclisation reaction to various nucleophiles could construct complex molecules.²³ We have recently showed that how dibenzoylacetylene can be used to construct multichromophoric heterocyclic systems with thiazolo[3,2-b]triazole, triazolo[1,5-a]pyrimidine, triazolo[3,4-b][1,3,4]thiadiazine, imidazo[2,1-b]thiazole and benzo[d]thiazolo[3,2-a]imidazole as core structures.^{23a,24} Taking advantage of the high isocyanide reactivity and inherent versatility of DBA, we report for the first time solvent-free

synthesis of 3, 4, 5-trisubstituted 2-aminofurans *via* a multicomponent approach from simple substrates such as aromatic aldehydes, DBA and isocyanides in which both 3 and 4 positions are functionalized with benzoyl group (scheme 1). To the best of our knowledge the synthesis of 3, 4, 5-trisubstituted 2-aminofurans so far has never been accomplished under solvent-free reaction conditions. The methodology is very simple, robust, energy efficient, high-yielding and applicable to a variety of aldehydes and isocyanides as starting materials.

Scheme 1. Solvent-free synthesis of 2-aminofurans

Initially, we carried out the reaction of 2-nitrobenzaldehyde **1a**, dibenzoylacetylene **2** and cyclohexyl isocyanide **3** by simply grinding **1a** and **2** together followed by the drop wise addition of **3**. The solid phase reacts within minutes to yield a sticky solid that hardens further on standing^{††}. The condensation product **4a** was obtained in excellent yields (91%) by simply washing the ground product with acetonitrile. ¹H NMR spectrum of **4a** exhibited characteristic signals at δ 1.39-2.09 (series of *multiplet*) for five CH₂ groups of the cyclohexyl moiety and a symmetric *multiplet* at δ 3.6 for the cyclohexyl methine H, along with characteristic aromatic signals at δ 7.05-7.88. The NH H-atom resonated at 8.2 (*d*, *J*=8.0 Hz) due to vicinal coupling with the cyclohexyl methine H-atom, supporting the IR absorption at 3430 cm⁻¹. The ¹H-decoupled ¹³C NMR spectrum showed 24 distinct resonances, with two benzoyl carbonyl carbons resonating at δ 189.65 and 191.06, in agreement with the proposed structure. The structure of the product **4a** was further authenticated by single crystal x-ray analysis (CCDC 1449548). As compared to the most conventional syntheses of substituted 2-aminofurans (up to 24 hours), our synthetic approach by solvent-free reaction conditions reached a substantial degree of conversion within 5–15 minutes (Fig 1). Surprisingly, the reaction was found to be exothermic as the reaction vessel became warm during the course of reaction. The heat evolved helps in the melting of solid and probably provides the necessary activation energy for the reaction. Hence, no external heating is required and the grinding method is used to accomplish reduction in particle size (greater surface area) and effective mixing. High intensity grinding is also not required as the reaction mixture does not remain dry and powdery but becomes a viscous liquid after the addition of isocyanide, which then hardens further on standing. Yields are appreciably higher using the solvent-free conditions as indicated in Table 1. To our delight, various substituted aromatic aldehydes with dibenzoylacetylene and cyclohexyl isocyanide gave the corresponding 3, 4, 5-substituted 2-aminofurans with good yields in all cases.

Fig 1 Progress of reaction (entry 1): **a**-aldehyde and DBA mixture before isocyanide addition, **b**-after the addition of isocyanide (b-d, within 5 mins of time), **e**-washing with solvent

Table 1 Reaction of aldehydes with DBA and cyclohexyl isocyanide

Entry	Aldehyde	Product	Yield (%) ^a
1			91
2			89

^aIsolated yield

In order to explore the scope of the methodology and the reactivity of aldehydes/dibenzoylacetylene further, the reaction was extended to *tert*-butyl isocyanide. *Tert*-butyl isocyanide also elicited the same reactivity pattern and the results are tabulated in table 2. Single crystal X-ray diffraction has been established for structures **6a** (CCDC 1449550) and **6b** (CCDC 1449551) (fig 2).

Fig 2 Single crystal x-ray structure of **4a** (CCDC 1449548), **4c** (CCDC 1449549), **6a** (CCDC 1449550) and **6b** (CCDC 1449551)

Table 2 Reaction of aldehydes with DBA and *tert*-butyl isocyanide

Entry	Aldehyde	Product	Yield(%) ^a
1			95
2			92
3			87
4			82
5			88
6			86

^aIsolated yield

A mechanistic rationale for the formation of aminofurans is presented in scheme 2. The reaction may involve the initial generation of a zwitterionic intermediate from isocyanide and DBA, which adds to the carbon-oxygen double bond of the aldehyde to yield an intermediate. Subsequently, this intermediate may undergo a [1, 5] H shift to yield an aminofuran

Scheme 2

Conclusions

In conclusion we have uncovered an efficient solvent-free method for the synthesis of 2-aminofurans at room temperature by the reaction of aldehydes, DBA and isocyanides. Short reaction time, high yields, easy work-up procedure, avoidance of toxic solvents and non-chromatographic separation are the important superiorities of this methodology and solvent-free approach make this procedure to be a green synthetic protocol. We believe that our novel synthetic approach will set up a new efficient and conducive route for the synthesis of 2-, 4-, 5-trisubstituted 2-aminofurans in modern synthetic methodologies.

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References and notes

[†]The E factor, introduced by Sheldon⁶ is defined as the ratio of the weight of waste to the weight of product.

^{**}Representative synthetic procedure of 2-aminofuran: a mixture of the appropriate aldehyde (1 mmol) and DBA (1.1 mmol) was grounded by means of a porcelain mortar and pestle at room temperature. The mixture was then poured into reaction vessel and isocyanide (1.1 mmol) was added by a syringe. For uniform mixing, the reaction vessel was shaken in between at regular intervals. The reaction was monitored at room temperature and left as such for about an hour in order to ensure completion of reaction. The resulting solid was washed two to three times with acetonitrile and dried in order to obtain the pure 2-amino furan. Reactions were aldehyde is liquid; in that case only DBA was crushed.

- (a) Singh, M. S.; Chowdhury, S. *RSC Advances*, **2012**, 2, 4547; (b) Ugi, I.; *Pure Appl. Chem.* **2001**, 73, 187 and references therein; (c) Multicomponent Reactions, ed. Zhu, J.; Bienayme, H. Wiley-VCH, Weinheim, Germany, **2005**; (d) Domling, A. *Chem. Rev.* **2006**, 106, 17; (e) D' Souza, D. M.; Mueller, T. J. J. *Chem. Soc. Rev.* **2007**, 36, 3169; (f) Cariou, C. C. A.; Clarkson, G. J.; Shipman, M. *J. Org. Chem.*, **2008**, 73, 9762; (g) Umkehrer, M.; Kalinski, C.; Kolb, J.; Burdack, C. *Tetrahedron Lett.* **2006**, 47, 2391; (h) Domling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, 39, 3168.
- (a) Isonitrile Chemistry, Ugi, I.; Ed.; Academic Press: New York, **1971**; (b) Ugi, I.; Domling, A.; Horl, W.; Endeavour **1994**, 18, 115.
- (a) Ugi, I.; Lohberger, S.; Karl, R.; In *Comprehensive Organic synthesis*; Trost, B. M.; Fleming, I. Eds.; Pergamon: Oxford, **1991**; Vol. 2, 1083; (b) Domling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, 39, 3168.
- (a) Wang, G.-W. *Chem. Soc. Rev.* **2013**, 42, 7668; (b) Gu, Y.; *Green Chem.* **2012**, 14, 2091; (c) Tanaka, K.; Toda, F.; *Solvent-free Organic Synthesis*; Wiley-VCH: Weinheim, **2003**; (d) Hern'andez, J. G.; Juaristi, E. *J. Org. Chem.* **2010**, 75, 7107; (e) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York **1998**; (f) Li, S.; Wang, J. -X.; Wen, X.; Ma, X. *Tetrahedron*, **2011**, 67, 849; (g) Nelson, W. M. *Green Solvents for Chemistry Perspectives and*

- Practice; Oxford University Press: Oxford, New York, **2003**; (f) Sheldon, R. A. *Green Chem.*, **2005**, 7, 267.
5. (a) Balme, G.; Bossharth, E.; Monteiro N. *Eur. J. Org. Chem.* **2003**, 4101; (b) Orru, R. V. A.; Greef, M. De. *Synthesis*, **2003**, 1471; (c) Bienaymé, H.; Hulme, C.; Odon, G.; Schmitt, P. *Chem. Eur. J.*, **2000**, 6, 3321; (d) Grondal, C.; Jeanty, M.; Enders, D.; *Nat. Chem.* **2010**, 2, 167; (e) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.*, **2006**, 45, 7134.
 6. Sheldon, R. A. *Chem. Ind.* 1992, 903.
 7. (a) Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Commun.* **2001**, 2159. (b) Metzger, J. O. *Angew. Chem. Int. Ed.*, **1998**, 37, 2975; (c) Tanaka, K.; Toda, F. *Chem. Rev.* 2000, 100, 1025; (d) Wang, Y.; Teng, X.; Wang, J.; Yang, H. *Nano Lett.*, **2003**, 3, 789.
 8. (a) Toda, F. *Acc. Chem. Res.* **1995**, 28, 480; (b) Ji, S. J.; Shen, Z. L.; Gu, D. G.; Huang, X. Y. *Ultrason. Sonochem.* **2005**, 12, 161; (c) Shen, Z. L.; Ji, S. J.; Loh, T. P. *Tetrahedron Lett.* 2005, **46**, 507; (d) Shen, Z. L.; Ji, S. J.; Zhou, W. J.; Yang, J. M. *Synth. Commun.* **2005**, 35, 1903; (e) Yang, J. M.; Ji, S. -J.; Gu, D. -G.; Shen, Z. L.; Wang, S.-Y. *J. Organomet. Chem.* **2005**, 690, 2989; (f) Jin, T. S.; Zhang, J. S.; Wang, A. Q.; Li, T. S. *Synth. Commun.* 2005, **35**, 2339; (g) Jin, T. S.; Feng, G. L.; Yang, M. N.; Li, T. S. *Synth. Commun.* **2004**, 34, 1277; (h) Ji, S. J.; Lu, J.; Zhu, X.; Yang, J.; Lang, J. P.; Wu, L., *Synth. Commun.* **2002**, 32, 3069; (i) Tu, S. J.; Wei, Q. H.; Ma, H. J.; Shi, D. Q.; Gao, Y.; Cui, G. Y. *Synth. Commun.* **2001**, 31, 2657; (j) Shen, Z. L.; Ji, S. J. *Synth. Commun.* **2009**, 39, 775; (k) Sheldon, R. A. *Pure Appl. Chem.* **2000**, 72, 1233.
 9. (a) Kirsch, S. F.; *Org. Biomol. Chem.* **2006**, 4, 2076; (b) Kumar, A.; Meneni, S. R. in Modern approaches to the synthesis of O- and N-heterocycles, ed. T. S. Kaufman and E. L. Larghi, Research Signpost, Trivandrum, India, 2007, vol. 1, pp. 1–23. (b) Brown, R. C. D. *Angew. Chem. Int. Ed.*, **2005**, 44, 850; (c) Hou, X.-L.; Yang Z.; Yeung, K.-S.; Wong, H. N. C. in Heterocyclic Chemistry, ed. W. G. Gordon and A. J. John, *Elsevier*, **2009**, vol. 21, pp. 179–223; (d) W. Dennis L, in *Heterocyclic Chemistry*, ed. W. G. Gordon and A. J. John, Elsevier, **2005**, vol. 17, pp. 1–32.
 10. (a) Petronijevic, F. R.; Wipf, P.; *J. Am. Chem. Soc.* **2011**, 133, 7704; (b) Trost, B. M.; McDougall, P. J. *Org. Lett.* **2009**, 11, 3782; (c) Medimagh, R.; Marque, S.; Prim, D.; Chatti, S.; Zarrouk, H. *J. Org. Chem.* **2008**, 73, 2191.
 11. (a) Boonsompat, J.; Padwa, A. *J. Org. Chem.*, **2011**, 76, 2753; (b) Zhang, H.; Boonsombat J.; Padwa A.; *Org. Lett.* **2006**, 9, 279.
 12. Kiren, S.; Hong, X.; Leverett, C. A.; Padwa, A. *Org. Lett.* **2009**, 11, 1233.
 13. Nicolaou, K. C.; Baran, P. S.; Zhong, Y. L.; Fong, K. C.; Choi, H. S. *J. Am. Chem. Soc.* **2002**, 124, 2190.
 14. (a) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. H.; *J. Org. Chem.* **1997**, 62, 4088.
 15. (a) LaPorte, M.; Hong, K. B.; Xu, J.; Wipf, P. *J. Org. Chem.* **2013**, 78, 167; (b) Li, G.; Padwa, A. *Org. Lett.* **2011**, 13, 3767.
 16. Erian, A. W.; Sherif, S. M.; Gaber, H. M. *Molecules*, **2003**, 8, 793.
 17. Liu, Lei, P. M.; Ma, L.; Hu, L. *Synlett.* **2011**, 1133.
 18. (a) Nair, V.; Vinod, A. U. *Chem. Commun.* **2000**, 1019; (b) Terzidis, M. A.; Stephanidou-Stephanatoum, J.; Tsoleridis, C. A. *J. Org. Chem.* **2010**, 75, 1948.
 19. Alizadeh, A.; Rostamnia, S.; Zhu, L.-G. *Synthesis*. **2008**, 1788.
 20. Mossetti, R.; Caprioglio, D.; Colombano, G.; Tron, G. C.; Pirali T. *Org. Biomol. Chem.* **2011**, 9, 1627.
 21. Jiang, Y.; Khong, V. Z. Y.; Lourdasamy, E.; Park, C.-M.; *Chem. Commun.* **2012**, 48, 3133.
 22. Huynh, T. N. T.; Retailleau, P.; Denhez, C.; Nguyen, K. P. P.; Guillaume, D. *Org. Biomol. Chem.* **2014**, 12, 5098.
 23. (a) Mir, N. A.; Shah, T. A.; Ahmad, S.; Muneer, M.; Rath, N. P.; Ahmad, M. *Tetrahedron letters.* **2014**, 55, 1706; (b) Lahiri, S.; Mahajan, M. P.; Prasad, R.; George, M. V. *Tetrahedron*, **1977**, 33, 3159.
 24. Shah, T. A.; Ahmad, Z.; Mir, N. A.; Muneer, M.; Rath, N. P.; Ahmad, M. *RSC Adv.*, **2015**, 5, 107931.