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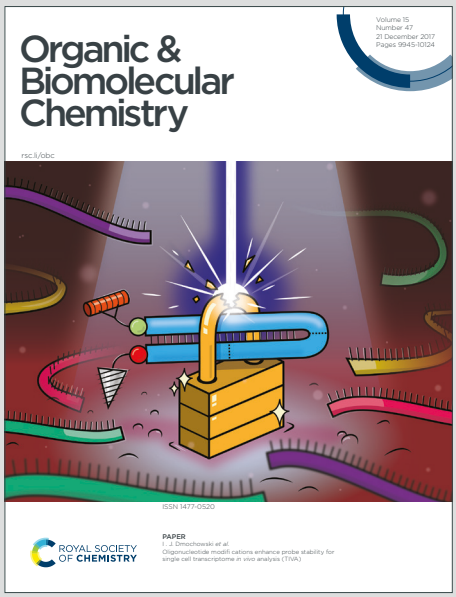

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Journal Name

COMMUNICATION

Novel one-pot method for the stereoselective synthesis of tetrahydropyrimidinones in low melting mixture

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A direct and metal free one-pot method has been developed for the stereoselective synthesis of tetrahydropyrimidinone derivatives from vinyl arene and formaldehyde using tartaric acid-dimethylurea (TA:DMU) melt as a green reaction medium. The substrate scope of this method is very general and the tetrahydropyrimidinone (THPM) derivatives are synthesized in good yields with high degree of diastereoselectivity. In this reaction, the melt plays a triple role as solvent, catalyst and reagent.

Heterocyclic motifs such as pyrimidinone derivatives are key structural units present in a wide variety of biologically active molecules.[1] The pyrimidinones are known to exhibit potent biological activities such as antiarrhythmic,[2] antihypertensive,[3] antibacterial,[4] antiproliferative[5] as well as calcium channel modulator.[6] Moreover, hydropyrimidinones exhibit antineoplastic[7] and anti-HIV activities[8] by inhibiting dihydroorotase and HIV-protease enzyme.[9–11] Similarly, monastrol (**1**)[12] exhibits potent antiproliferative activity by inhibiting kinesin Eg5, a molecular motor protein, which is responsible for the formation of bipolar spindle during cell division. In addition, piperastrol (**6**) displays antiproliferative activity against HT-29 (colon) and MCF-7 (breast) cell lines,[14] whereas pyrimidinone-hybrid molecule (**7**), derived from dihydropyrimidinone (DHPM) and palmitic fatty acid, exhibits potent antiproliferative activity against gliomas cell line (Figure 1).[15]

The chromopynones are glucose uptake inhibitors that target glucose transporters Glut-1 and 3, and thus stop the growth of cancer cell. Intriguingly, tetrahydropyrimidinones (THPMs) have also served as precursors in the biology-oriented synthesis (BIOS) of pseudo natural chromopynones.[16]

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†Electronic Supplementary Information (ESI) available: General procedure, experimental details and crystallographic data. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

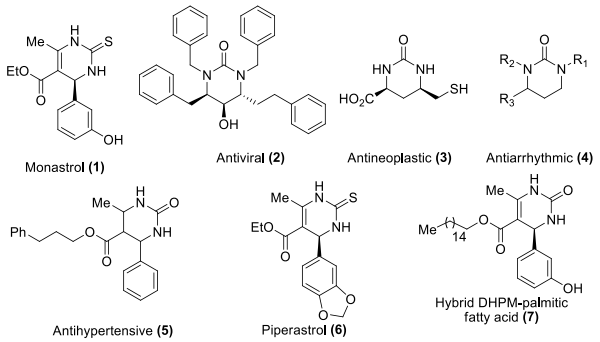
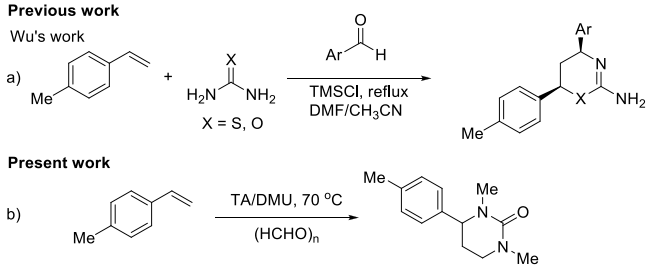


Fig. 1 Pyrimidinone based biologically important molecules.

Various metal mediated methods have been developed for the synthesis of THPM derivatives, which include $W(CO)_6$ catalyzed oxidative carbonylation of diamine,[17] ZnO mediated synthesis of cyclic urea derivatives under microwave conditions,[18] palladium-catalyzed synthesis of tetrahydropyrimidinones,[19] indium facilitated synthesis of hexahydro-pyrimidine from alkene and formaldimines,[20] and iridium assisted hydrogenation of pyrimidines.[21] In 2006, Wu and co-worker reported TMSCl mediated reaction of alkene with iminium ion, derived from aldehyde and urea/thiourea, furnished the corresponding 2-amino-4,5-dihydro-1,3-oxazine/1,3-thioazine derivatives (Scheme 1a).[22] Nevertheless, development of a simple and efficient approach for the synthesis of THPMs is highly desirable due to their broad spectrum of biological activities.



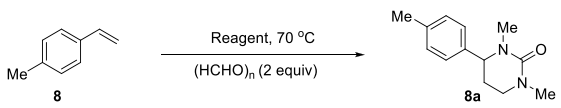
Scheme 1 Synthesis of heterocyclic compounds from vinyl arene.

Low-melting mixture as a reaction medium is an emerging area in organic synthesis due to their interesting physicochemical

properties.[23] Low-melting mixture, a sustainable reaction medium, consists of nontoxic, non-volatile and biodegradable compounds readily available from natural resources. Thus, the synthetic versatility of eutectic mixtures as novel green reaction medium is expanding very rapidly.[24] Herein, we describe a three-component based approach for the synthesis of THPM derivatives using environmentally benign low melting mixture as a green reaction medium.[25]

We anticipated that an iminium ion, derived from urea and aldehyde, upon addition to alkene followed by *in situ* cyclization would provide an easy and direct access to tetrahydropyrimidinone derivative. To test our assumption, 4-methyl styrene (**8**) was treated with formaldehyde in citric acid-dimethylurea (CA:DMU) melt at 70 °C and the resultant mixture was stirred at the same temperature for 26h. To our delight, upon work-up it afforded tetrahydropyrimidinone derivative (**8a**) in 37% yield. The structure of **8a** was unambiguously established on the basis of ^{1}H NMR, ^{13}C NMR, HRMS, and IR analyses. In order to optimize the reaction conditions, different melt combinations were explored and the results are summarized in Table 1. Among the melts screened, the tartaric acid- dimethylurea (TA:DMU) melt was found to be the most effective green reaction medium for the synthesis of THPM derivative (Table 1, entry 2).

Table 1 Optimization of reaction conditions[a]



Entry	Reagent	Time (h)	Yield (%)[b]
1	CA:DMU(4:6) melt	26	37
2	TA:DMU(3:7) melt	22	53
3[c]	TA:ChCl(1:2) melt	29	42
4[d]	TFA:DMU in DCE	30	0

[a]Reaction conditions: A mixture of 4-methyl styrene (1 equiv) and formaldehyde (2 equiv) was used in 1.5g of melt. [b]Yield based on the isolated product. [c]DMU (1.5 equiv) was added. [d]A mixture of TFA (1 equiv) and DMU (2 equiv) was used in DCE.

After optimizing the reaction conditions, the generality of this methodology was examined with various substrates and the results are summarized in Table 2. Under the reaction conditions, the substituted styrene derivatives **9, 10, 11, 12** and **13** afforded the corresponding THPM derivatives **9a, 10a**, **11a, 12a** and **13a,** respectively, in good yields (Table 2, entries 1-4).[26] Under similar reaction conditions, 1-(allyloxy)-4-vinylbenzene (**14**) afforded THPM derivative **14a** as the only product in good yield (Table 2, entry 5). Intriguingly, the allyl ether functional group was found to be stable under the reaction conditions and moreover the unactivated alkene moiety did not participate in the pyrimidinone reaction.

Unlike simple alkene, the electron rich 3,4-dihydropyran (**21**) reacted readily under the conditions to furnish bicyclic tetrahydropyrimidinone derivative **21a** in good yield (Table 2,

Table 2 Synthesis of tetrahydropyrimidinone in L-(+)-tartaric acid and dimethylurea melt

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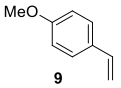
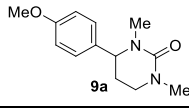
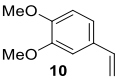
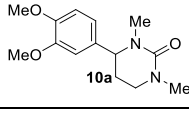
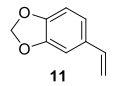
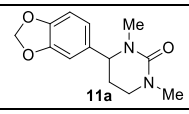
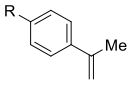
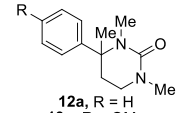
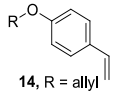
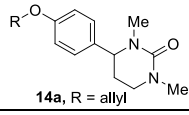
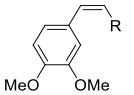
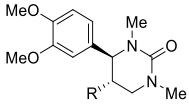
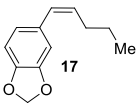
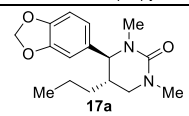
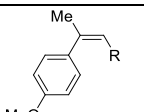
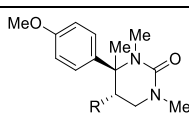
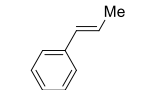
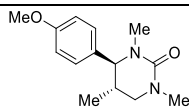
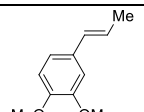
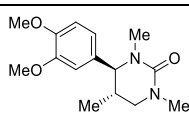
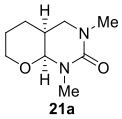
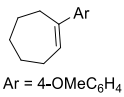
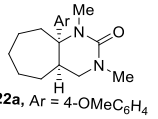
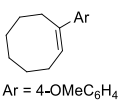
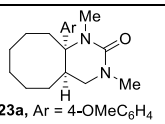
Entry	Starting material	Product	Time (h)	Yield (%) (dr)
1	 **9**	 **9a**	22	59
2	 **10**	 **10a**	14	76
3	 **11**	 **11a**	17	68
4	 **12**, R = H **13**, R = OMe	 **12a**, R = H **13a**, R = OMe	23 21	69 76
5	 **14**, R = allyl	 **14a**, R = allyl	22	73
6	 **15**, R = Me **16**, R = n-propyl	 **15a**, R = Me **16a**, R = n-propyl	20 21	63 (19:1) 73 (19:1)
7	 **17**	 **17a**	18	68 (19:1)
8	 **18**, R = n-propyl	 **18a**, R = n-propyl	24	69 (19:1)
9	 **19**	 **19a**	20	72 (19:1)
10	 **20**	 **15a**	16	81 (19:1)
11	 **21**	 **21a**	16	66
12	 **22**, Ar = 4-OMeC$_6$H$_4$	 **22a**, Ar = 4-OMeC$_6$H$_4$	14	80
13	 **23**, Ar = 4-OMeC$_6$H$_4$	 **23a**, Ar = 4-OMeC$_6$H$_4$	17	74

[a]Reaction conditions: styrene (1 equiv), formaldehyde (2 equiv) in TA:DMU(3:7, w/w) melt at 70 °C. Yield based on isolated product.

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entry 11). Similarly, electron rich 1-aryl-cycloalkene derivatives **22** and **23** afforded the corresponding bicyclic THPM derivatives **22a** and **23a,** respectively, in very good yields (Table 2, entries 12 & 13).

Encouraged by these observations, the scope of this reaction was further tested with 1,2-disubstituted styrene derivatives. Under the melt reaction conditions, *cis*-vinyl arene derivative **15** underwent smooth reaction to furnish *trans*-4,5-disubstituted tetrahydropyrimidinone derivative **15a** as the only product in good yield (Table 2, entry 6). Remarkably, both *cis*- and *trans*-1,2-disubstituted vinyl arene derivatives **15**-**20** underwent smooth reaction to furnish *trans*-4,5-disubstituted THPM derivatives **15a**-**19a**, respectively, in good yields with excellent diastereoselectivity (dr = 19:1) (Table 2, entries 6-10). The exclusive formation of *trans*-diastereomer can be attributed to the generation of stable benzylic carbocation.

Based on these observations, a plausible mechanism for the formation of THPM is shown in Figure 2. The iminium ion **A**, derived from formaldehyde and dimethylurea, would react with vinyl arene to generate a stable benzylic carbocation **B**, which on subsequent intramolecular cyclization could then lead to THPM derivative.

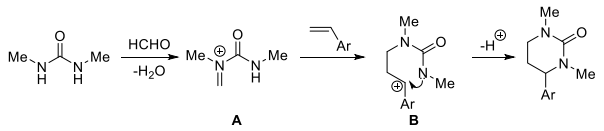
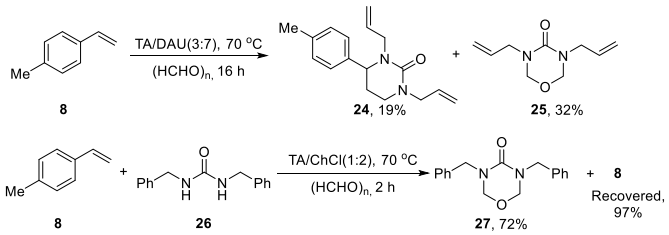


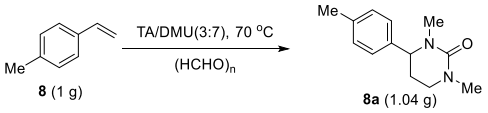
Fig. 2 Plausible mechanism for the formation of THPM derivative.

Moreover, under tartaric acid-diallylurea (TA:DAU) melt conditions, 4-methyl styrene (**8**) reacted with formaldehyde at 70 °C to furnish the corresponding bis-allyl THPM derivative **24** in 19% yield along with 3,5-diallyl-1,3,5-oxadiazinan-4-one (**25**) in 32% yield. However in TA:ChCl melt,[27] dibenzylurea reacted readily to furnish 3,5-dibenzyl-1,3,5-oxadiazinan-4-one (**27**) as the only product in 72% yield (Scheme 2).[28]



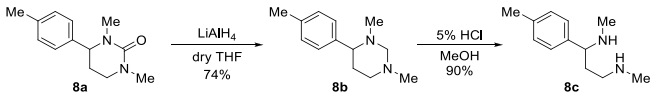
Scheme 2 Reaction of diallylurea and dibenzylurea under melt conditions.

To demonstrate the scalability of this method, a gram-scale reaction was performed with vinyl arene **8** under optimized reaction conditions. The gram-scale reaction proceeded smoothly and provided the corresponding THPM derivative **8a** in 56% yield which was in good agreement with the small-scale reaction. Moreover, the melt medium can be recovered and recycled. Using recovered melt, the THPM derivative (**8a**) was isolated in 49% yield.



Scheme 3 Gram-scale synthesis of THPM derivative **8a**.

The 1,3-diamine functionality is a ubiquitous structural feature present in a wide range of natural products and pharmaceuticals.[29] The six-membered cyclic urea, tetrahydropyrimidinone **8a** on $LiAlH_4$ reduction followed by acid hydrolysis afforded 1-aryl-1,3-diamine **8c** in very good yield (Scheme 4).[30]



Scheme 4 Synthesis of 1,3-diamine.

In summary, a mild and highly efficient protocol has been developed for the synthesis of tetrahydropyrimidinones using tartaric acid-DMU melt as a novel reaction medium. Under these conditions, vinyl arenes reacted readily with formaldehyde to furnish THPM derivatives in good yields with high degree of diastereoselectivity. In this reaction, melt plays a triple role as solvent, catalyst as well as reagent.

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Notes and references

1 (a) G. V. De Lucca, J. Liang, P. E. Aldrich, J. Calabrese, B. Cordova, R. M. Klabe, M. M. Rayner and C.-H. Chang, *J. Med. Chem.*, 1997, **40**, 1707; (b) B. Pasquier, Y. El-Ahmad, B. Filoche-Romme, C. Dureuil, F. Fassy, P.-Y. Abecassis, M. Mathieu, T. Bertrand, T. Benard, C. Barriere, S. El Batti, J.-P. Letallec, V. Sonnefraud, M. Brollo, L. Delbarre, V. Loyau, F. Pilorge, L. Bertin, P. Richepin, J. Arigon, J.-R. Labrosse, J. Clement, F. Durand, R. Combet, P. Perraut, V. Leroy, F. Gay, D. Lefrancois, F. Bretin, J.-P. Marquette, N. Michot, A. Caron, C. Castell, L. Schio, G. McCort, H. Goulaouic, C. Garcia-Echeverria and B. Ronan, *J. Med. Chem.*, 2015, **58**, 376; (c) M. Gichinga, J. P. Olson, E. Butala, H. A. Navarro, B. P. Gilmour, S. W. Mascarella and F. I. Carroll, *ACS Med. Chem. Lett.*, 2011, **2**, 882; (d) M. Vijjulatha and S. S. Kanth, *Cent. Eur. J. Chem.*, 2007, **5**, 1064; (e) P. Babczinski, M. Blunck, G. Sandmann, K. Shiokawa and K. Yasui, *Pestic. Biochem. Physiol.*, 1995, **52**, 45.

2 US Pat., WO93/04060, March 4, 1993.

3 G. C. Rovnyak, K. S. Atwal, A. Hedeberg, S. D. Kimball, S. Moreland, J. Z. Gougoutas, B. C. O'Reilly, J. Schwartz and M. F. Malley, *J. Med. Chem.*, 1992, **35**, 3254.

4 (a) V. Ramachandran, P. Ramesh, K. Arumugasamy, S. K. Singh, N. Edayadulla and S.-K. Kamaraj, *J. Chem. Biol.*, 2016, **9**, 31; (b) S. Shaikh, N. P. Shaikh, S. D. Salunke, and M. A. Baseer, *Heterocycl. Lett.*, 2015, **5**, 443; (c) S. Baluja, R. Gajera, and S. Chanda, *J. Bacteriol Mycol.*, 2017, **5**, 414.

5 D. Russowsky, R. F. S. Canto, S. A. A. Sanches, M. G. M. D'Oca, A. de Fatima, R. A. Pilli, L. K. Kohn, M. A. Antonio and J. E. de Carvalho, *Bioorg. Chem.*, 2006, **34**, 173.

6 (a) C. O. Kappe, *Molecules*, 1998, **3**, 1; (b) B. Jauk, T. Pernat, and C. O. Kappe, *Molecules*, 2000, **5**, 227.

7 (a) P. K. Jadhav, P. Ala, F. J. Woerner, C.-H. Chang, S. S. Garber, E. D. Anton and L. T. Bacheler, *J. Med. Chem.*, 1997, **40**, 181; (b) G. V. De Lucca, J. Liang and I. De Lucca, *J. Med.*

Chem., 1999, **42**, 135; (c) J. L. Adams, T. D. Meek, S. M. Mong, R. K. Johnson and B. W. Metcalf, *J. Med. Chem.*, 1988, **31***,* 1355.

8 (a) M. E. Pierce, G. D. Harris, Q. Islam, L. A. Radesca, L. Storace, R. E. Waltermire, E. Wat, P. K. Jadhav, and G. C. Emmett, *J. Org. Chem.*, 1996, **61***,* 444; (b) P. Gayathri, V. Pande, R. Sivakumar and S. P. Gupta, *Bioorg. Med. Chem.*, 2001, **9***,* 305; (c) A. R. Katritzky, A. Oliferenko, A. Lomaka and M. Karelson, *Bioorg. Med. Chem. Lett.*, 2002, **12***,* 3453.

9 D. W. Pettigrew, R. R. Bidigare, B. J. Mehta, M. I. Williams and E. G. Sander, *Biochem. J.*, 1985, **230***,* 101.

10 (a) R. Garg and B. Bhhatarai, *Bioorg. Med. Chem.*, 2004, **12***,* 5819; (b) C. N. Hodge, P. E. Aldrich, L. T. Bacheler, C. H. Chang, C. J. Eyermann, S. Garber, M. Grubb, D. A. Jackson, P. K. Jadhav, B. Korant, P. Y. Lam, M. B. Maurin, J. L. Meek, M. J. Otto, M. M. Rayner, C. Reid, T. R. Sharpe, L. Shum, D. L. Winslow and S. Erickson-Viitanen, *Chem. Biol.*, 1996, **3***,* 301.

11 P. Y. Lam, Y. Ru, P. K. Jadhav, P. E. Aldrich, G. V. De Lucca, C. J. Eyermann, C. H. Chang, G. Emmett, E. R. Holler, W. F. Daneker, L. Li, P. N. Confalone, R. J. McHugh, Q. Han, R. Li, J. A. Markwalder, S. P. Seitz, T. R. Sharpe, L. T. Bacheler, M. M. Rayner, R. M. Klabe, L. Shum, D. L. Winslow, D. M. Kornhauser, D. A. Jackson, S. Erickson-Viitanen and C. N. Hodge, *J. Med. Chem.*, 1996, **39***,* 3514.

12 T. U. Mayer, T. M. Kapoor, S. J. Haggarty, R. W. King, S. L. Schreiber and T. J. Mitchison, *Science*, 1999, **286***,* 971.

13 M. Gartner, N. Sunder-Plassmann, J. Seiler, M. Utz, I. Vernos, T. Surrey, and A. Giannis, *ChemBioChem*, 2005**, 6***,* 1173.

14 M. A. Bhat, A. Al-Dhfyan and M. A. Al-Omar, *Molecules*, 2016, **21***,* 1746.

15 (a) T. G. M. Treptow, F. Figueiro, E. H. F. Jandrey, A. M. O. Battastini, G. C. Salbego, J. B. Hoppe, P. S. Taborda, S. B. Rosa, L. A. Piovesan, C. D. R. D'Oca, D. Russowsky and M. G. Montes D'Oca, *Eur. J. Med. Chem.*, 2015, **95***,* 552; (b) F. S. De Oliveira, P. M. De Oliveira, L. M. Farias, R. C. Brinkerhoff, R. C. M. A. Sobrinho, T. M. Treptow, C. R. Montes D'Oca, M. A. G. Marinho, M. A. Hort, A. P. Horn, D. Russowsky and M. G. Montes D'Oca, *MedChemComm*, 2018, **9***,* 1282.

16 G. Karageorgis, E. S. Reckzeh, J. Ceballos, M. Schwalfenberg, S. Sievers, C. Ostermann, A. Pahl, S. Ziegler and H. Waldmann, *Nat. Chem.*, 2018, **10**, 1103.

17 F. Qian, J. E. McCusker, Y. Zhang, A. D. Main, M. Chlebowski, M. Kokka and L. McElwee-White, *J. Org. Chem.*, 2002, **67**, 4086.

18 Y. J. Kim and R. S. Varma, *Tetrahedron Lett.*, 2004, **45**, 7205.

19 (a) M. Morgen, S. Bretzke, P. Li and D. Menche, *Org. Lett.*, 2010, **12**, 4494; (b) Y. Nishikawa, S. Kimura, Y. Kato, N. Yamazaki and O. Hara, *Org. Lett.*, 2015, **17**, 888.

20 (a) I. M. Taily, D. Saha and P. Banerjee, *Eur. J. Org. Chem.*, 2019, **2019**, 7804; (b) H. Zhou, H. H. Chaminda Lakmal, J. M. Baine, H. U. Valle, X. Xu and X. Cui, *Chem. Sci.*, 2017, **8**, 6520.

21 G.-S. Feng, L. Shi, F.-J. Meng, M.-W. Chen and Y.-G. Zhou, *Org. Lett.*, 2018, **20**, 6415.

22 Y. Zhu, S. Huang, J. Wan, L. Yan, Y. Pan and A. Wu, *Org. Lett.*, 2006, **8**, 2599.

23 (a) Q. Zhang, K. De Oliveira Vigier, S. Royer and F. Jerome, *Chem. Soc. Rev.*, 2012, **41**, 7108; (b) C. Russ and B. König, *Green Chem.*, 2012, **14**, 2969.

24 Organic transformation in melt (a) A. Punzi, D. I. Coppi, S. Matera, M. A. M. Capozzi, A. Operamolla, R. Ragni, F. Babudri and G. M. Farinola, *Org. Lett.*, 2017, **19**, 4754; (b) M. J. Rodriguez-Alvarez, C. Vidal, J. Diez and J. Garcia-Alvarez, *Chem. Commun.*, 2014, **50**, 12927; (c) C. Vidal, L. Merz and J. Garcia-Alvarez, *Green Chem.*, 2015, **17**, 3870.

25 (a) S. Gore, S. Baskaran and B. König, *Green Chem*., 2011, **13***,* 1009; (b) S. Gore, S. Baskaran and B. König, *Adv. Synth. Catal.*, 2012, **254***,* 2368; (c) S. Gore, S. Baskaran, and B. König, *Org. Lett.* 2012, **14***,* 4568; (d) S. Gore, K. Chinthapally, S. Baskaran, and B. König, *Chem. Commun.*, 2013, **49**, 5052.

26 In the case of simple styrene, the reaction was found to be very sluggish and the corresponding THPM derivative was isolated in 14% yield.

27 Surprisingly, dibenzylurea did not form melt with tartaric acid even at 150 °C.

28 A. P. Venkov and T. A. Temnyalova, *Synth. Commun.*, 1996, **26**, 3217.

29 (a) N. B. Pham, S. Deydier, M. Labaied, S. Monnerat, K. Stuart and R. J. Quinn, *Eur. J. Med. Chem.*, 2014, **74**, 541-551; (b) T. Kammermeier and W. Wiegrebe, *Arch Pharm*, 1995, **328,** 409; (c) X. Ji and H. Huang, *Org. Biomol. Chem.*, 2016, **14**, 10557; (d) Y. Liu, Y. Xie, H. Wang and H. Huang, *J. Am. Chem. Soc.*, 2016, **138**, 4314; (e) J. Hu, Y. Xie and H. Huang, *Angew. Chem., Int. Ed.*, 2014, **53**, 7272.

30 (a) H. A. Bates, N. Condulis and N. L. Stein, *J. Org. Chem.*, 1986, **51**, 2228; (b) A. R. Pradipta and K. Tanaka, *Bull. Chem. Soc. Jpn.*, 2016, **89**, 337.