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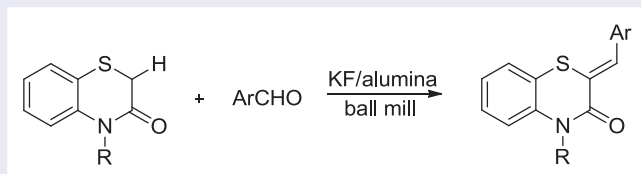
Synergistic promoting effect of ball milling and KF–alumina support as a green tool for solvent-free synthesis of 2-arylidene-benzothiazinones

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ABSTRACT

A solvent-free procedure is developed for the reaction of benzothiazinones with benzaldehyde derivatives, where the solid KF–Al₂O₃ support and ball milling synergistically leads to a green and efficient synthesis of several 2-arylidene-benzothiazinones. Therefore, a cooperative effect of the solid support and ball milling leads to excellent yields of the target dienes, while the catalyst can be recycled for subsequent reactions without significant loss of its activity.



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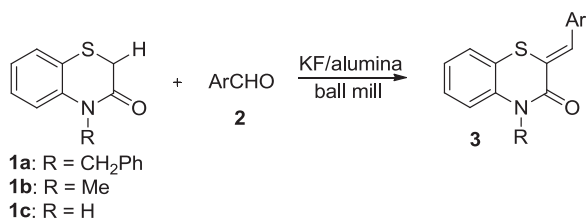
1. Introduction

Considerable effort has been devoted in recent decades by synthetic chemists to design and develop green processes.[1] This has led to increasing use of environmentally cleaner solvents, reagents, and catalysts [2] and as a result an everyday growth has been witnessed in the development of solvent-free procedures [3,4] and solid-supported synthesis.[5,6] Nowadays, solid-support catalyzed reactions constitute a very powerful synthetic tool in organic chemistry.[7] In specific, potassium fluoride on alumina (KF–Al₂O₃) has been used as a very popular system since KF–Al₂O₃ possesses a mild basic character, exhibits increased reactivity and selectivity in its reactions, and requires no special work-up conditions.[8,9]

On another green chemistry front, many investigations have been carried out in a search for new energy source for activation of reactants for various transformations. This has led to the development of useful synthetic methods involving the adoption of microwave [10]

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Scheme 1. Optimization of the conditions for the synthesis of **3a**.

and ultrasonic [11,12] techniques. Another rapidly growing alternative energy sources has been ball milling,[13,14] a method which provides the required energy via mechanical grinding of the reactants in solid form and has succeeded in emerging as a green method for conducting different synthetic reactions.[13,15]

The 2-arylidene-benzothiazinones constitute a class of heterocyclic compounds which are significant for their antimalarial,[16] medicinal,[17,18] aldose reductase inhibition,[19] and anti-bacterial [20] properties. In addition, they have potential as precursors in constructing more complex heterocyclic structures via dipolar [21] and Diels-Alder cycloaddition reactions,[22] further simultaneously being useful for the synthesis of larger benzothiazepine rings.[23] Perhaps the most efficient and straightforward route for the synthesis of these dienes goes through the Knoevenagel condensation of the respective benzothiazinones with aromatic aldehydes,[24,25] although they have also been obtained via ring contraction of 1,4-thiazepin-5-one [26,27] or Horner–Wadsworth–Emmons reactions.[28,29]

In continuation of our investigations to develop environmentally attractive synthetic procedures [30,31] and in the framework of our studies on heterocyclic systems,[32,33] we here report a synergistic phenomenon caused by concurrent use of KF–alumina support and ball milling which promotes the solvent-free synthesis of a group of (*Z*)-2-arylidene-benzothiazinone derivatives **3**, as shown in Scheme 1 for the reaction between benzothiazinones **1** and aromatic aldehydes **2** to produce dienes **3**.

2. Results and discussion

Initially the condensation of **1a** with benzaldehyde **2a** was chosen as the model reaction to optimize the conditions (Table 1). A 1.0:1.0 solvent-free mixture of the two reactants was shaken at 20 Hz in a ball mill reactor for 70 min gave no products (Entry 1). Addition of 1.0 mmol of either alumina (Entry 2) or KF (Entry 3) to this mixture produced 18% or 25% of **3a**, respectively, after the same time period. When both KF and alumina were used together the yield increased to 40% (Entry 4), while the same mixture without ball milling gave only 20% of **3a** (Entry 5), indicating the crucial effect of ball milling in the process.

For further optimization of the conditions for the synthesis of **3a**, we examined the influence of ball milling, catalyst, and the time on the reaction progress, as summarized in Table 2. Thus, an improved yield for **3a** was observed when the reaction was carried out at a frequency of 30 Hz (Table 2, Entry 1). Variation in the catalyst amount indicated that 1.5 mmol of KF–alumina is the optimum amount (Entries 2–5). Similarly, the best ratio for **1a/2a** was determined to be 1.0:1.5 (Entries 6 and 7). Under the optimized ratio of the reactants and the reagent (1.0:1.5:1.5), the optimum reaction time at 30 Hz was demonstrated to be 50 min (Entries 6–9).

Table 1. Study the effect of catalyst on solvent-free synthesis of **3a**.

Entry	Catalyst	Time (min)	Yield (%) ^{a,b}
1	None	70	–
2	Alumina	70	18
3	KF	70	25
4	KF–alumina	70	40
5	KF–alumina	70 ^b	20

^aIsolated yield.^bNo ball milling.**Table 2.** Optimization of the synthesis of **3a**.

Entry	1a:2a :catalyst	Time (min)	Yield (%) ^a
1	1.0:1.0:1.0	50	47
2	1.0:1.0:0.8	50	42
3	1.0:1.0:1.2	50	55
4	1.0:1.0:1.5	50	57
5	1.0:1.0:2.0	50	57
6	1.0:1.5:1.5	50	92
7	1.0:2.0:1.5	50	70
8	1.0:1.5:1.5	25	51
9	1.0:1.5:1.5	40	62

^aIsolated yield.

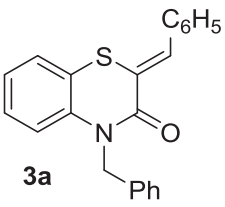
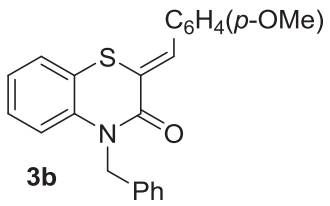
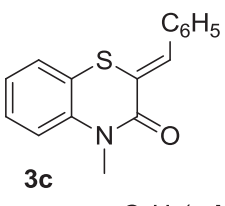
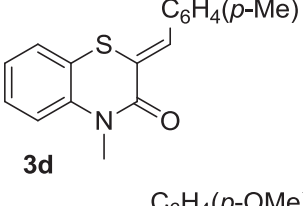
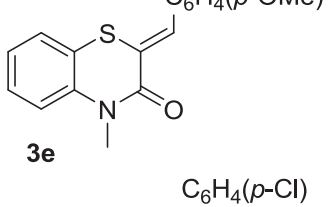
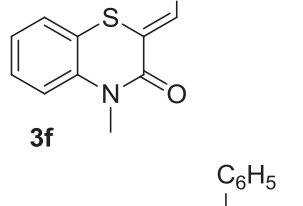
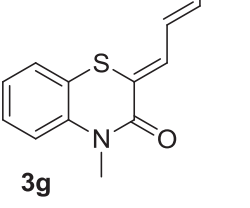
To extend the scope of the reaction, we then applied the optimized conditions to various substrates, as summarized in Table 3. Besides the reaction with benzaldehyde (Entry 1), **1a** reacted with *p*-methoxybenzaldehyde as well to produce **3b** (Entry 2). The *N*-Me substituted benzothiazinone derivative **1b** also reacted successfully under the optimized conditions to efficiently produce products **3c–3g** (Entries 3–7). This was also the case for the reactions of the unsubstituted reactant **1c** with **2a–b** (Entries 8 and 9). In all cases, NMR spectroscopy verified the structure of the products.

The reusability of the catalyst was studied next, where the recovered KF–Al₂O₃ was reused several times in the reaction between **1a** and **2a** (Figure 1). For this reason, the suspension of the reaction mixture in ethyl acetate was filtered to separate the catalyst. The recovered catalyst was then dried and reactivated in a microwave oven (360 watt) for 5 min before being reused in the subsequent runs and without any makeup. As a result, it could be reused for four runs with only showing a gradual decrease in its activity after each recovery.

3. Conclusion

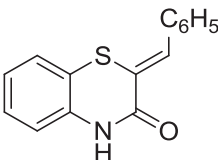
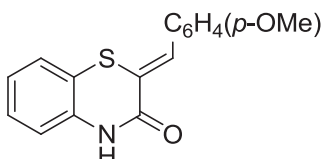
In summary, a versatile benign route to product **3** is developed which under solvent-free conditions leads to high yields of 2-arylidene-benzothiazinones. The attractive features of the procedure are the mild reaction conditions, the use of acid-free reagents, and to overall very low waste generation. These make the method a useful and attractive green addition to the literature archive for the preparation of the target compounds. For a more direct comparison, some previously reported conditions used to produce compounds similar to those reported here are presented in Table 4.

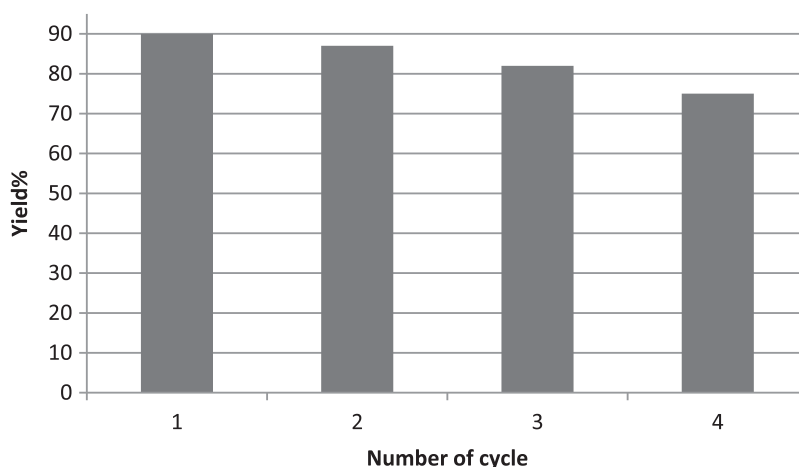
Table 3. Evaluation of the reaction scope.

Entry	Reactants	Product	Time (min)	Yield (%) ^a	Mp (°C)
1	1a + C ₆ H ₅ CHO	 3a	50	92	71–73 (this work)
2	1a + <i>p</i> -MeOC ₆ H ₄ CHO	 3b	65	90	110–112 (this work)
3	1b + C ₆ H ₅ CHO	 3c	50	92	86–88 [28]
4	1b + <i>p</i> -MeC ₆ H ₄ CHO	 3d	60	90	138–139 [28]
5	1b + <i>p</i> -MeOC ₆ H ₄ CHO	 3e	60	88	101–104 (this work)
6	1b + <i>p</i> -ClC ₆ H ₄ CHO	 3f	65	87	120–122 (this work)
7	1b + C ₆ H ₅ CH = CHCHO	 3g	65	85	109–111 [28]

(Continued)

Table 3. Continued.

Entry	Reactants	Product	Time (min)	Yield (%) ^a	Mp (°C)
8	1c + C ₆ H ₅ CHO	 3h	55	87	201–203 [28]
9	1c + <i>p</i> -MeOC ₆ H ₄ CHO	 3i	80	90	207–210 [28]

^aIsolated yield.**Figure 1.** The reusability of the catalyst for the synthesis of **3a**.**Table 4.** Comparison of the present procedure with some other recent methods.

Entry	Method	Condition (Reference)	Yield%
1	Knoevenagel condensation	(i) SO ₂ Cl ₂ , CH ₂ Cl ₂ (2–5 h); (ii) triethyl phosphite, reflux (28 h); (iii) C ₂ H ₅ OH, NaOEt [28]	50–94
2	Ring contraction	C ₅ H ₅ N, SOCl ₂ , rt (2d), 55°C (4 h) [26]	14
3	Horner-Wadsworth-Emmons reaction	DMF, NaOMe (excess), 125°C, 3 h [24]	69
4	Knoevenagel condensation	KF–Alumina, Ball mill, rt, 45 min (This work)	87–92

4. Experimental design

Reactions were monitored by thin-layer chromatography (TLC). FT-IR spectra were recorded using KBr disks on a Bruker Vector-22 infrared spectrometer and absorptions were reported as wave numbers (cm⁻¹). NMR spectra were obtained on an FT-NMR Bruker Ultra Shield™ (500 MHz) as CDCl₃ solutions and the chemical shifts were expressed

as δ units with Me_4Si as the internal standard. Mass spectra were obtained on a Finnigan Mat 8430 apparatus at ionization potential of 70 eV. Elemental analyses were performed by a Thermo Finnigan Flash EA 1112 instrument. Compounds **1** were prepared using available methods. All other chemicals were purchased from commercial sources and were freshly used after being purified by standard procedures.

4.1. Typical synthesis of **3**

A 5 mL stainless steel vial was charged with a derivative of benzothiazinones **1** (1.0 mmol), benzaldehyde **2a** (1.5 mmol) and KF–alumina (0.24 g) together with a 10 mm stainless steel ball. The vial was sealed with a Teflon gasket. The reaction was shaken at 30 Hz in an oscillatory ball mill for the appropriate length of time. After completion of the reaction, based on TLC monitoring, the crude reaction mixture was diluted with ethyl acetate (10 mL) and filtered to separate the catalyst. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography using silica gel and EtOAc/hexanes mixture (1/10) as the eluent. The identity of known products was confirmed by comparison of their spectroscopic data with those available in the literature. New products were characterized by ^1H NMR, ^{13}C NMR, IR, CHN and mass spectra and their purity was confirmed by elemental analysis.

4.2. Spectral data of new products

4.2.1. (Z)-4-Benzyl-2-benzylidene-2H-benzo[b][1,4]thiazin-3(4H)-one (**3a**)

Yellow solid; 71–73 $^\circ\text{C}$; IR (KBr) 3032, 1632, 1583, 1485, 1439 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.03 (s, 1H), 7.71 (d, $J = 7.5$ Hz, 2H), 7.50 (t, $J = 7.5$ Hz, 2H), 7.44–7.38 (m, 3H), 7.32–7.29 (m, 4H), 7.11–7.09 (dt, $J = 1.5, 7.5$ Hz, 1H), 7.05 (d, $J = 7.5$ Hz, 1H), 7.00 (d, $J = 7.5$ Hz, 1H), 5.41 (s, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 162.6, 137.2, 136.9, 135.6, 135.2, 130.7, 129.4, 129.3, 128.8, 127.6, 127.4, 126.7, 126.6, 124.0, 121.0, 119.8, 117.9, 49.8; MS (70 eV) m/z 343 (M^+), 252, 224, 102, 91, 77; Anal. Calcd for $\text{C}_{22}\text{H}_{17}\text{NOS}$: C, 76.94; H, 4.99; S, 9.34. Found: C, 76.59%; H, 4.78%; S, 9.15%.

4.2.2. (Z)-4-Benzyl-2-(4-methoxybenzylidene)-2H-benzo[b][1,4]thiazin-3(4H)-one (**3b**)

Yellow solid; 110–112 $^\circ\text{C}$; IR (KBr) 3039, 2339, 1622, 1492, 1292 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.91 (s, 1H), 7.66 (d, $J = 8.5$ Hz, 2H), 7.34 (dd, $J = 8.0, 8.0$ Hz, 2H), 7.25 (m, 4H), 7.07 (t, $J = 8.0$ Hz, 1H), 6.99–6.92 (m, 4H), 5.35 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 163.1, 160.6, 137.4, 137.0, 135.5, 132.6, 129.3, 128.0, 127.6, 127.4, 126.7, 126.6, 123.9, 120.0, 118.2, 117.9, 114.4, 55.8, 49.8; Anal. Calcd for $\text{C}_{23}\text{H}_{19}\text{NO}_2\text{S}$: C, 73.97; H, 5.13; S, 8.59. Found: C, 74.115; H, 4.995; S, 8.75%.

4.2.3. (Z)-2-(4-Methoxybenzylidene)-4-methyl-2H-benzo[b][1,4]thiazin-3(4H)-one (**3e**)

Yellow solid; 101–104 $^\circ\text{C}$; IR (KBr) 2954, 2312, 1631, 1495 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.83 (s, 1H), 7.62 (d, $J = 8.5$ Hz, 2H), 7.25–7.19 (m, 2H), 7.03–6.98 (m, 2H), 6.95 (d, $J = 8.5, 2\text{H}$), 3.83 (s, 3H), 3.53 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 163.4, 160.5, 138.1, 135.1, 132.5, 127.9, 127.4, 126.7, 123.7, 119.9, 118.3, 116.9, 114.3, 55.7, 33.2;

MS (70 ev) m/z 297 (M^+), 264, 190, 159, 136, 108; Anal. Calcd for $C_{17}H_{15}NO_2S$: C, 68.66; H, 5.08; S, 10.78. Found: C, 68.89%; H, 4.92%; S, 10.84%.

4.2.4. (Z)-2-(4-Chlorobenzylidene)-4-methyl-2H-benzo[b][1,4]thiazin-3(4H)-one (3f)

Yellow solid; mp 120–122°C; IR (KBr) 3429, 2904, 1643, 1471 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.28–7.24 (m, 2H), 7.10–7.03 (m, 2H), 3.57 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 137.8, 135.1, 133.8, 133.6, 131.9, 129.1, 128.7, 127.6, 126.8, 123.9, 119.2, 117.1, 33.3; MS (70 ev) m/z 301 (M^+), 268, 190, 136; Anal. Calcd for $C_{16}H_{12}ClNOS$: C, 63.68; H, 4.01; S, 10.62. Found: C, 63.81%; H, 4.11%; S, 10.75%.

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References

- [1] Anastas PT, Warner JC. Green chemistry: theory and practice. Oxford: Oxford University Press; 1998.
- [2] Tundo P, Perosa A, Zecchini F. Methods and reagents for green chemistry. Hoboken, NJ: John Wiley & Sons; 2007.
- [3] Garay AL, Pichon A, James SL. Solvent-free synthesis of metal complexes. Chem Soc Rev. 2007;36:846–855.
- [4] Tanaka K. Solvent-free organic synthesis. 2nd ed. Weinheim: Wiley-VCH; 2009.
- [5] Sheldon RA, van Bekkum H. Fine chemicals through heterogeneous catalysis. Weinheim: Wiley-VCH; 2001.
- [6] Sherrington DC, Kybett AP. Supported catalysts and their applications. Cambridge: Royal Society of Chemistry; 2001.
- [7] Blass BE. KF/Al_2O_3 mediated organic synthesis. Tetrahedron. 2002;58:9301–9320.
- [8] Moghaddam FM, Bardajee GR. Microwave-assisted β -elimination of sulfoxides on KF/Al_2O_3 support under solvent-free conditions. J Sulfur Chem. 2005;26:325–329.
- [9] Mizar P, Myrboh B. Three-component synthesis of 5:6 and 6:6 fused pyrimidines using KF -alumina as a catalyst. Tetrahedron Lett. 2008;49:5283–5285.
- [10] Polshettiwar V, Varma RS. Microwave-assisted organic synthesis and transformations using benign reaction media. Acc Chem Res. 2008;41:629–639.
- [11] Mojtahedi MM, Abaee MS. Ultrasound applications in synthetic organic chemistry. In: Chen D, Sharma SK, Mudhoo A, editors. Handbook on applications of ultrasound: sonochemistry for sustainability. New York: CRC Press; 2012. p. 281–321.
- [12] Mamaghani M, Pourranjbar M, Hossein Nia R. Facile and regioselective synthesis of thiazolidin-4-one derivatives catalyzed by basic ionic liquid [bmim]OH under ultrasonic irradiation. J Sulfur Chem. 2014;35:1–6.
- [13] Rodríguez B, Bruckmann A, Rantanen T, Bolm C. Solvent-free carbon-carbon bond formations in ball mills. Adv Synth Catal. 2007;349:2213–2233.
- [14] Nasir Baig RB, Varma RS. Alternative energy input: mechanochemical, microwave and ultrasound-assisted organic synthesis. Chem Soc Rev. 2012;41:1559–1584.
- [15] Zhu SE, Li F, Wang GW. Mechanochemistry of fullerenes and related materials. Chem Soc Rev. 2013;42:7535–7570.
- [16] Preuss J, Maloney P, Peddibhotla S, et al. Discovery of a *plasmodium falciparum* glucose-6-phosphate dehydrogenase 6-phosphogluconolactonase inhibitor (*R,Z*)-*N*-((1-ethylpyrrolidin-2-yl)methyl)-2-(2-fluorobenzylidene)-3-oxo-3,4-dihydro-2*H*-benzo[b][1,4]thiazine-6-carboxamide (ML276) that reduces parasite growth in vitro. J Med Chem. 2012;55:7262–7272.

- [17] Kawashima Y, Ota A, Mibu H, Santen Pharmaceutical Co., Ltd. 3-Oxo-1,4-benzothiazine derivatives. United States patent US 5,496,817. 1996 Mar 5.
- [18] Kawashima Y, Ota A, Morikawa Y, Santen Pharmaceutical Co., Ltd. 3-Oxo-1,4-benzothiazine derivatives. United States patent US 5,547,952. 1996 Aug 20.
- [19] Aotsuka T, Hosono H, Kurihara T, Nakamura Y, Matsui T, Kobayashi F, Sapporo Breweries Limited. 1,4-Benzothiazine-2-acetic acid derivatives. United States patent US 5,252,571. 1993 Oct 12.
- [20] Krapcho J, ER Squibb & Sons, Inc. Benzothiazine derivatives. United States patent US 3,725,403. 1973 Apr 3.
- [21] Lakshmi NV, Tamilsai R, Perumal PT. A facile synthetic approach to novel spiro-oxindoles/acenaphthylen-1-ones containing benzo[1,4]thiazin-3-one ring via 1,3-dipolar cycloaddition. *Tetrahedron Lett.* 2011;52:5301–5307.
- [22] Kamila S, Koh B, Zhang H, Biehl ER. Synthesis of (Z)-hetaryl-methylene and (Z)-substituted benzylidene derivatives of 4*H*-benzo[1,4]thiazine-3-thiones and their subsequent conversion to benzothioapyrano-[3,2-*b*][1,4]benzothiazines. *Arkivoc.* 2006;ii:1–14.
- [23] Maki Y, Sako M, Mitsumori N, Maeda S, Takaya M, Hamari Chemicals, Ltd. 1,5-Benzothiazepine derivatives and production thereof. United States patent US 4,490,292. 1984 Dec 25.
- [24] Alves Souza AM, Pádua Walfrido ST, Costa Leite LF, Alves Lima MC, Rocha Pitta SLGI. Efficient synthesis of benzothiazine and acrylamide compounds. *Quim Nova.* 2010;33:562–565.
- [25] Guarda VLM, Pereira MA, De Simone CA, et al. Synthesis and structural study of arylidene thiazolidine and benzothiazine compounds. *Sulfur Lett.* 2003;26:17–27.
- [26] Kugita H, Inoue H, Ikezaki M, Taked S. Synthesis of 1,5-benzothiazepinederivatives. *Chem Pharm Bull.* 1970;18:2028–2037.
- [27] Erker T, Bartsch H. Untersuchungen zur ringverengung von 1,5-benzothiazepinen zu 1,4-benzothiazinen. *Liebigs Ann Chem.* 1992;403–405.
- [28] Worley JW, Wayne Ratts K, Cammack KL. 2-Dialkylphosphonyl- and 2-alkylidene-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazines. *J Org Chem.* 1975;40:1731–1734.
- [29] Molteni V, He X, Nabakka J, et al. Identification of novel potent bicyclic peptide deformylase inhibitors. *Bioorg Med Chem Lett.* 2004;14:1477–1481.
- [30] Sharifi A, Ansari M, Darabi HR, Abaee MS. Synergistic promoting effect of ball milling and KF-alumina support for the green synthesis of benzothiazinones. *Tetrahedron Lett.* 2016;57:429–532.
- [31] Sharifi A, Abaee MS, Rouzgard M, Mirzaei M. [Omim][NO₃], a green and base-free medium for one-pot synthesis of benzothiazinones at room temperature. *Synth Commun.* 2013;43:2079–2089.
- [32] Abaee MS, Cheraghi S. Efficient three-component Gewald reactions under Et₃N/H₂O conditions. *J Sulfur Chem.* 2014;35:261–269.
- [33] Abaee MS, Mahmoudi F, Forghani S, Mojtahedi MM, Harms K. Efficient synthesis of novel bis(arylmethylidenes) of the 2,2-dimethyl-1,3-dithian-5-one system. *J Sulfur Chem.* 2016;37. in press. doi:10.1080/17415993.2015.1130131.