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.

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]...
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     | 70b        | 40           |
| 5     | KF–alumina     | 70b        | 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 (%) | Mp (°C)        |
|-------|----------------------------|-----------------------|------------|-----------|----------------|
| 1     | 1a + C₆H₅CHO               | ![Structure 3a](image) | 50         | 92        | 71–73 (this work) |
| 2     | 1a + p-MeOC₆H₄CHO          | ![Structure 3b](image) | 65         | 90        | 110–112 (this work) |
| 3     | 1b + C₆H₅CHO               | ![Structure 3c](image) | 50         | 92        | 86–88 [28]       |
| 4     | 1b + p-MeC₆H₄CHO           | ![Structure 3d](image) | 60         | 90        | 138–139 [28]     |
| 5     | 1b + p-MeOC₆H₄CHO          | ![Structure 3e](image) | 60         | 88        | 101–104 (this work) |
| 6     | 1b + p-ClC₆H₄CHO           | ![Structure 3f](image) | 65         | 87        | 120–122 (this work) |
| 7     | 1b + C₆H₅CH=CHCHO          | ![Structure 3g](image) | 65         | 85        | 109–111 [28]     |

(Continued)
Table 3. Continued.

| Entry | Reactants | Product | Time (min) | Yield (%)<sup>a</sup> | Mp (°C) |
|-------|-----------|---------|------------|------------------------|---------|
| 8     | 1c + C₆H₅CHO | ![3h](image) | 55         | 87                     | 201–203[28] |
| 9     | 1c + p-MeOC₆H₄CHO | ![3i](image) | 80         | 90                     | 207–210[28] |

<sup>a</sup> Isolated 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) SO₂Cl₂, CH₂Cl₂ (2–5 h); (ii) triethyl phosphate, reflux (28 h); (iii) C₆H₅OH, NaOEt [28] | 50–94  |
| 2     | Ring contraction | C₅H₅N, SOCl₂, 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<sup>−1</sup>). NMR spectra were obtained on an FT-NMR Bruker Ultra Shield<sup>®</sup> (500 MHz) as CDCl<sub>3</sub> solutions and the chemical shifts were expressed
as δ units with Me₄Si 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, ¹³C 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 mp°C; IR (KBr) 3032, 1632, 1583, 1485, 1439 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125MHz, CDCl₃) 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 C₂₂H₁₇NOS: 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 mp°C; IR (KBr) 3032, 1632, 1583, 1485, 1439 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.91 (s, 1H), 7.66 (d, J = 8.5 Hz, 2H), 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), 5.35 (s, 2H), 3.86 (s, 3H); ¹³C NMR (125MHz, CDCl₃) δ 163.1, 160.6, 137.4, 137.0, 135.5, 132.6, 129.3, 128.0, 127.6, 127.4, 126.7, 123.9, 120.0, 118.2, 117.9, 114.4, 55.8, 49.8; Anal. Calcd for C₂₃H₁₉NO₂S: 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 mp°C; IR (KBr) 2954, 2312, 1631, 1495 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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, 2H), 3.83 (s, 3H), 3.53 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) 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$_2$S: 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$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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%.

Acknowledgement

Authors would like to thank the Analytical Chemistry Department for conducting some of the analysis experiments.

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