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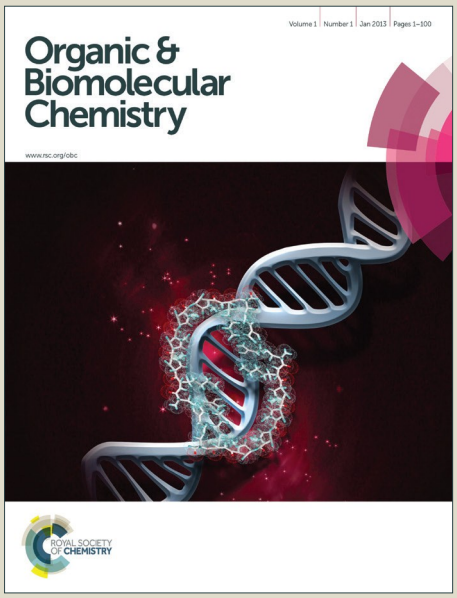

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Mechanochemical Solid-State Synthesis of 2-Aminothiazoles, Quinoxalines and Bezoylbenzofurans from Ketones by One-Pot Sequential Acid- and Base-Mediated Reactions

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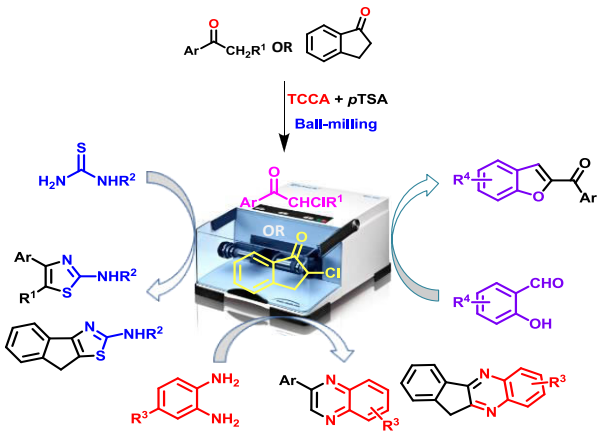
ABSTRACT

α-Chloroketones–accessed by atom-economic chlorination of ketones with trichloroisocyanuric acid (TCCA) in the presence of *p*-TSA under ball-milling condition–were set up for sequential base–mediated condensation reaction with thiourea/thiosemicarbazides, *o*-phenylenediamine and salicyladehyde to afford 2-aminothiazoles, 2-hydrazinylthiazole, quinoxalines and benzoylbenzofurans, respectively, in respectable yields. The viability of one-pot sequential acid– and base–mediated reactions in the solid state under ball-milling condition is thus demonstrated.

GRAPHIC FOR TOC



Diverse 2-aminothiazoles, quinoxalines and benzofurans are accessed in respectable yields by one-pot solid-state sequential acid- and base-mediated reactions under ball milling conditions.

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INTRODUCTION

Heterocyclic 2-aminothiazoles,[1] quinoxalines[2] and benzofurans[3] have been widely used in medicinal chemistry[4] and agriculture.[5] They have been found to exhibit diverse biological properties such as antibacterial,[6] antiviral,[7] anticancer,[8] anti-inflammatory,[9] etc. In Chart 1 are shown a few select examples of pharmaceutical drugs containing aminothiazole, quinoxaline and benzofuran moieties.[4c,6d,10] Further, they constitute the core nuclei of molecular systems that are building blocks of different functional materials, e.g., organic light emitting diodes (OLEDs),[11] organic semiconductors, solar cells, dyes, etc.[12] Insofar as their synthesis is concerned, the approach based on 2-halocarbonyl compounds as starting materials is the most attractive one.[13] Direct synthetic protocols based on starting materials such as ketones,[14] α,β-unsaturated ketones,[14c] alkenes,[15] etc. via the intermediary α-haloketones have been reported for aminothiazoles. Additionally, the syntheses of quinoxaline[16] and benzofuran[17] derivatives have also been reported. These synthetic procedures, however, are associated with certain disadvantages such as heating, hazardous reaction conditions, formation of side products, tedious work-up procedures, etc.

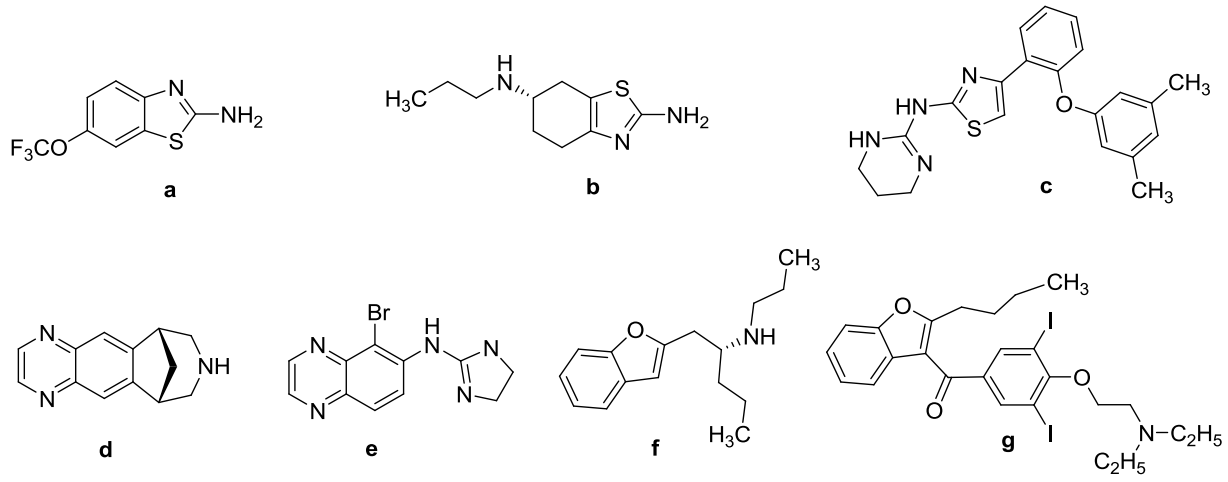

Chart 1. Select examples of biologically-active compounds containing aminothiazole, quinoxaline and bezoylbenzofuran moieties: (a) riluzole[10a] (antiglutamate), (b) pramipexole[4b] (antidepressant), (c) abafungin[4b] (antifungal), (d) varenicline[16b] (smoking abstinent), (e) brimonidine[10b] (intraocular antihypertensive), (f) (-)-BPAP[6d] (antidepressant), and (g) cordarone[6d] (antiarrhythmic agent).

We recently showed that α-halogenation of carbonyl compounds occurs in a facile manner under solvent-free ball-milling conditions using trichloroisocyanuric acid (TCCA)/*p*-TSA. Some of the advantageous attributes of TCCA as a chlorinating agent are: it is stable, cheap, readily available and environmentally

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benign.[18,19] More importantly, it serves as a source of three chlorine atoms to permit atom economy that is not rivaled by other chlorination reagents. Indeed, TCCA is popular as a high-purity chlorine source compared to hypochlorite.[20] We were, therefore, motivated to investigate further the reactions of α-chlorocarbonyl compounds–available by solid-state ball-milling reactions–to access 2-aminothiazoles, quinoxalines and benzofurans. Of course, our objectives at the outset were to explore the viability of sequential acid– and base–catalyzed reactions in the solid state and develop one-pot solvent-free synthesis of the aforementioned heterocycles under ball-milling conditions as an alternative to the solution-state synthesis. Mechanochemical ball-milling is a superlative greener technique that is increasingly becoming popular in organic synthesis.[21] Herein, we report the results of successful one-pot solid-state synthesis of various derivatives of 2-aminothiazole, quinoxaline and benzofuran by sequential acid- and base-mediated reactions under ball milling conditions in respectable isolated yields without isolation of the intermediary α-chloroketones.

RESULTS AND DISCUSSION

Synthesis of 2-Aminothiazole Derivatives. As mentioned earlier, we have shown in our previous investigations that α-chlorination of carbonyl compounds occurs conveniently under ball-milling conditions with TCCA/*p*-TSA (25 mol%) as the reagent system; indeed, TCCA was found to be better than the corresponding bromo-analog, namely, tribromoisocyanuric acid (TBCA), for α-bromination. We wondered if sequential α-chlorination of ketones followed condensation reaction with thiourea could be carried out in one pot under ball-milling conditions to afford 2-aminothiazoles. In a representative reaction, crystalline *p*-bromoacetophenone, 0.4 molar equiv of TCCA and 0.5 molar equiv of *p*-TSA were introduced into a 5 mL jar and subjected to milling with 6 balls to produce α-chloro-*p*-bromoacetophenone at a pre-fixed oscillation frequency of 20 Hz. After completion of α-chlorination over a period of 2 h, as judged by TLC analysis, thiourea (1.05 equiv) and K_2CO_3 (1.5 equiv) were introduced into the same jar. The solid reaction mixture was subjected to milling for further 4 h. Remarkably, the work-up followed by isolation led to 2-amino-4-(*p*-bromophenyl)thiazole in 90% yield (**2a**, Scheme 1). It is noteworthy that the two sequential reactions require acidic and basic conditions, respectively. The excellent isolated yield of the aminothiazole demonstrates the fact that sequential reactions are amenable to solid-state ball milling protocols.[22]

In a similar manner, the ball-milling reactions with *N*-arylated thioureas were found to occur in a facile manner, yielding the corresponding *N*-arylaminothiazoles in 83–86% isolated yields (**2b-f**, Scheme 1). Further, the reactions with 1-phenyl-3-thiosemicarbazide, 1-(*p*-bromophenyl)-3-thiosemicarbazide and 1-(*p*-methoxyphenyl)-3-thiosemicarbazide with α-chloro-*p*-bromoacetophenone–generated by TCCA/*p*-

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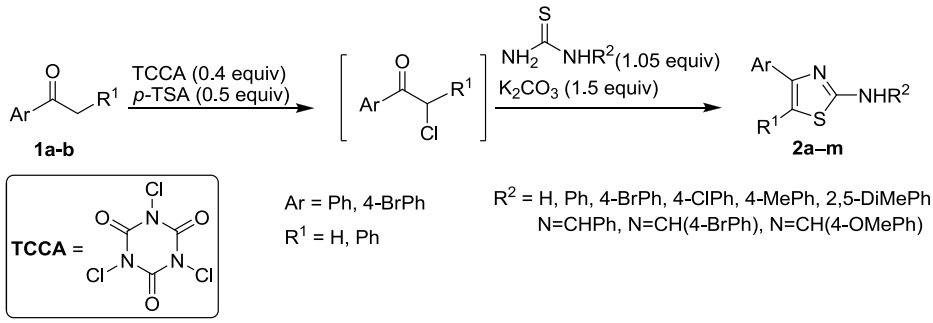
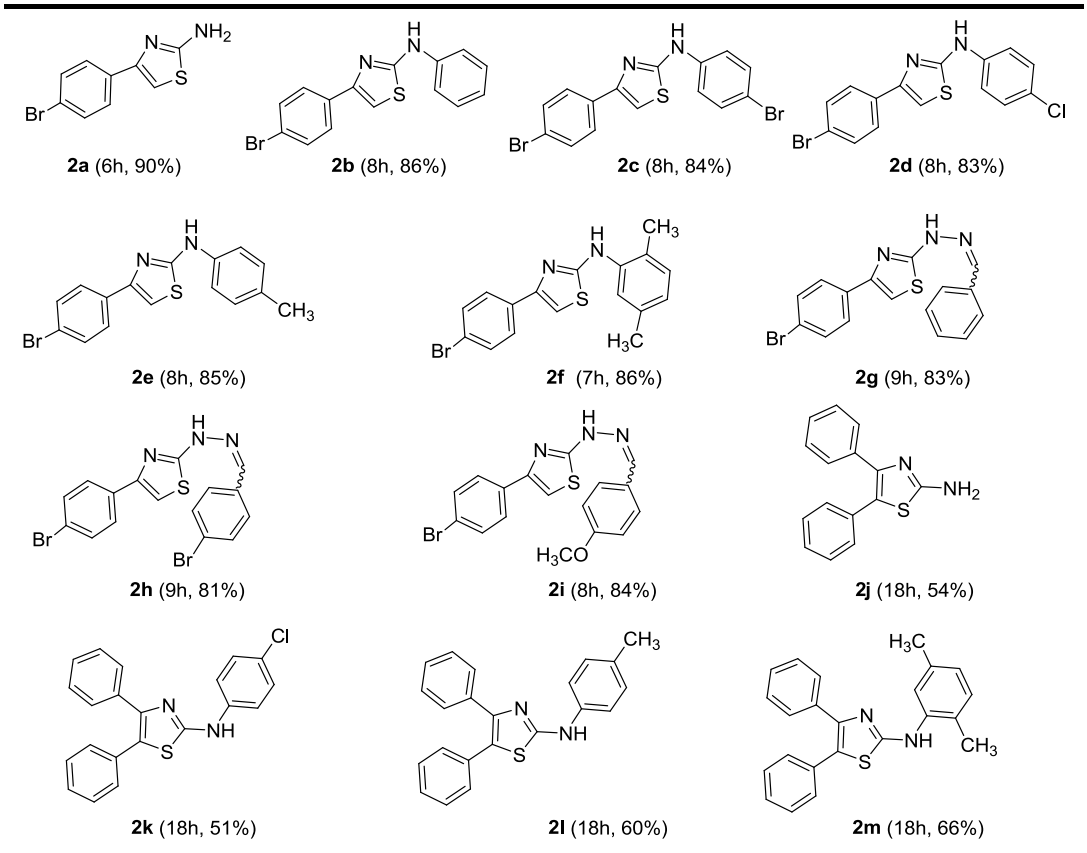
TSA reaction of *p*-bromoacetophenone–afforded respective 2-hydrazinylthiazoles in excellent isolated yields of 83, 81 and 84%, respectively in 8–9 h of milling (**2g-i**, Scheme 1). The reactions of benzyl phenyl ketones were, however, slow and occurred over longer durations leading to the corresponding products **2j-m** in isolated yields of 51–66%.

Scheme 1. Synthesis of 2-aminothiazole derivatives by consecutive α-halogenation followed by base-mediated condensation reactions under ball milling conditions at rt.[a]





[a] All reactions were performed without any extra precaution. Six balls were employed and the reactions were run with an oscillation frequency (ν_{osc}) of 20 Hz.

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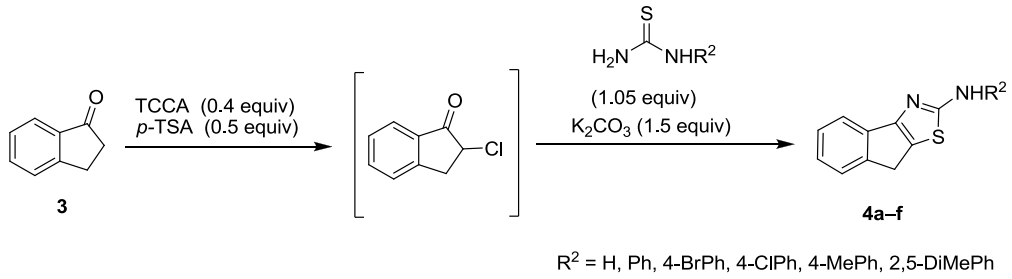
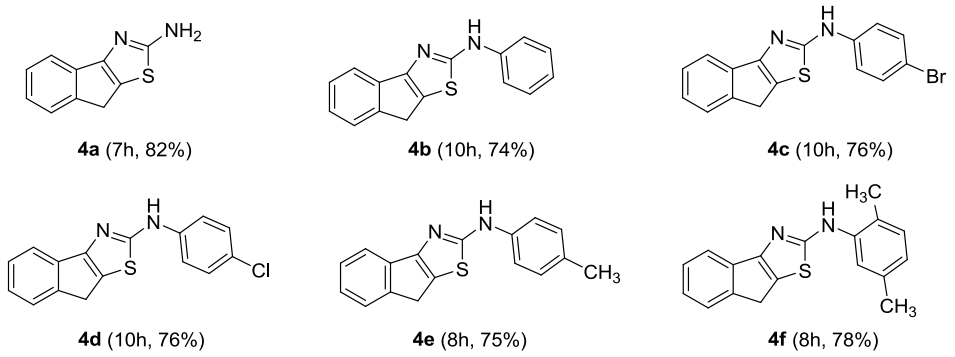
The same protocol could be extended to the synthesis of 2-amino-8*H*-indeno[1,2-*d*]thiazole derivatives, for which only a few methodologies requiring high temperatures, e.g., heating at 100 °C in ethanol, have been reported.[14a,b] Thus, the reaction of indanone with TCCA/*p*-TSA under ball milling at rt followed by treatment with urea/*N*-arylurea in the presence of K_2CO_3 led to 2-amino-8*H*-indeno[1,2-*d*]thiazole (**4a**) and its *N*-aryl derivatives (**4b-e**, Scheme 2) in 74–82% isolated yields. It should be noted that the chlorination of indanone led to a mixture of products, i.e., 2-chloroindanone and 2,2-dichloroindanone, both of which react with thiourea/*N*-arylthiourea leading to the aminoindenothiazole or its *N*-aryl derivative.

Scheme 2. Solid-state synthesis of 2-amino-8*H*-indeno[1,2-*d*]thiazole and its derivatives by consecutive α-halogenation and condensation reactions under ball milling conditions at rt.[a]





[a] all reactions were performed without any extra precaution. Six balls were employed and an oscillation frequency (ν_{osc}) of 20 Hz was maintained throughout the reaction.

Synthesis of Quinoxalines. The reactions of α-haloketones with *o*-phenylenediamines in the presence of K_2CO_3 in acetonitrile are known to furnish quinoxalines.[16b] Thus, α-chloro-*p*-bromoacetophenone, generated by solid-state ball-milling with TCCA/*p*-TSA, was reacted with *o*-phenyelendiamine/K_2CO_3 in a sequential manner as was done above, cf. Scheme 3. Indeed, the reaction was found to occur nicely at rt leading to 2-(*p*-bromophenyl)quinoxaline (**5a)** in 78% isolated yield. When 3-methyl-1,2-diaminobenzene was employed, a regioisomeric 50:50 mixture of the methyl derivatives of 2-(*p*-bromophenyl)quinoxaline, i.e., **5b** and **5b'**, was isolated in 82% yield. Likewise, chlorination of cyclic indanone followed by

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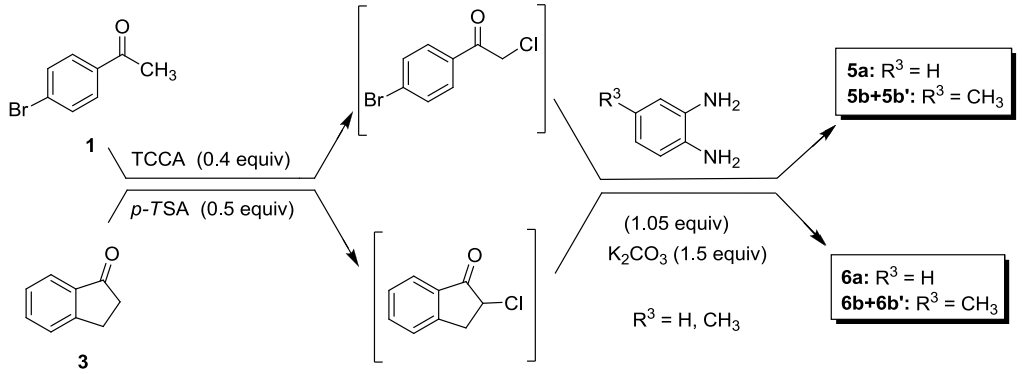
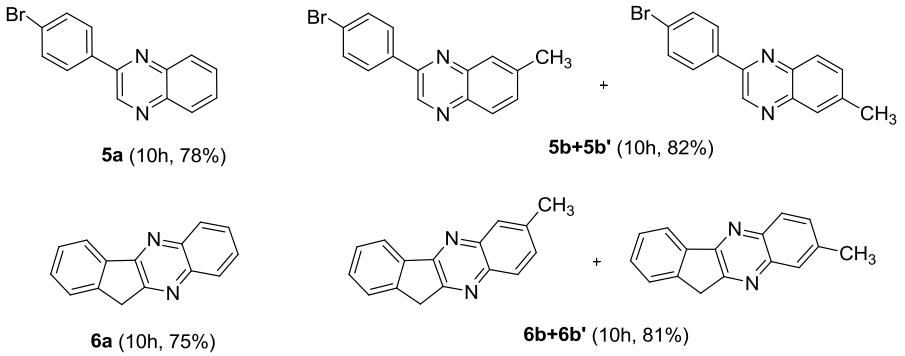
condensation with *o*-phenylenediamines yielded the corresponding 11*H*-indeno[2,1-*b*]quinoxalines (**6**, Scheme 3) 75–81% isolated yields. In this case, the initial reaction of halogenation led to a gummy reaction mixture. Therefore, neutral alumina was employed as a milling auxiliary. As in the case of *p*-bromoacetophenone, a regioisomeric mixture of products, i.e., **6b** and **6b'**, was isolated when 3-methyl-*o*-phenylenediamine was employed, cf. Scheme 3; ^{1}H NMR analysis of the mixture revealed the ratio between **6b** and **6b'** to be ca. 1:1. Separation of these isomers by silica gel column chromatography was unsuccessful despite several attempts.

Scheme 3. Synthesis of quinoxaline derivatives by sequential halogenation and condensation reactions under ball milling conditions at rt. [a]





[a] all reactions were performed without any extra precaution. Six balls were employed and an oscillation frequency (ν_{osc}) of 20 Hz was maintained throughout the reaction. [b] In the case of indanone, the reaction mixture became gummy. Therefore, neutral alumina was employed as a milling auxiliary, cf. text

Synthesis of 2-Benzoylbenzofurans. As shown in Scheme 4, the one-pot reaction of α-chloro-*p*-bromoacetophenone–generated from *p*-bromoacetophenone with TCCA/*p*-TSA–with salicylaldehyde led to hydroxy-ketone intermediate. Of course, under the basic conditions of the reaction, the dehydration reaction was found to be too sluggish. When the reaction was continued with addition of excess *p*-

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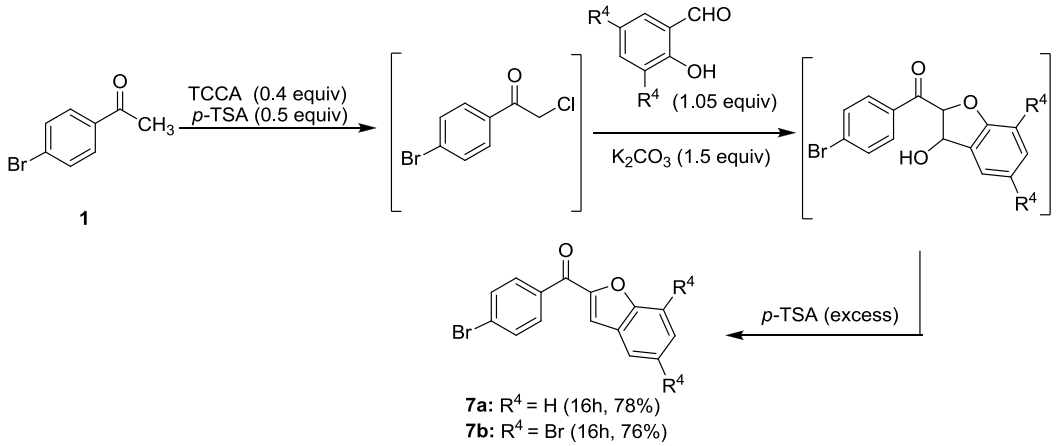
TSA–in amounts that nullifies the base and is present in excess to perform acid-catalyzed dehydration–bezoylbenzofuran (**7a**) was isolated in a remarkable yield of 78%. The one-pot reaction sequence with *p*-bromoacetopheone and 3,5-dibromosalicylaldehyde led to the corresponding (*p*-bromobenzoyl)bromobenzofuran (**7b**) in 76% isolated yield. Extension of this protocol to other substrates was limited by the necessity of ketones being crystalline and reactive for initial chlorination under ball milling conditions. Otherwise, the limited examples illustrate the occurrence of 3 consecutive reactions requiring acid, base and acid conditions in one pot.

Scheme 4. Synthesis of benzoylbenzofuran derivatives by sequential acid–base–acid mediated reactions under ball milling conditions at room temperature.[a]



CONCLUSIONS

We have exploited facile α-chlorination reaction of ketones with the atom-economic TCCA reagent under ball-milling conditions to explore the viability of sequential reactions in the solid-state for one-pot synthesis of medicinally important heterocycles. It is shown that α-chlorination followed by condensations with thiourea and *N*-arylthiourea lead to 2-aminothiazoles and 2-hydrazinylthiazoles in very good isolated yields. In the same manner, the reactions of α-chloroketones with *o*-phenylenediamines in a sequential manner are shown to lead to quinoxalines in respectable isolated yields. Limited cases of sequential acid-base-acid mediated halogenation, condensation and dehydration reactions are demonstrated to access benzoylbenzofurans. The occurrence of three tandem reactions–each mediated by an acid or base–is thus exemplified in the solid state under ball-milling conditions.

Electronic Supplementary Information Available. ^{1}H and ^{13}C NMR spectral reproductions of all products.

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EXPERIMENTAL SECTION

Materials and Methods

All reactions were carried out in a Retsch MM 200 ball mill. The products were isolated by column chromatography over silica gel (100−200 μm) using distilled solvents. ^{1}H and ^{13}C NMR spectra were recorded with JEOL 400 and 500 MHz spectrometers. FT-IR spectra were run on a Perkin Elmer spectrometer. Mass spectra were recorded with Waters ESI-^{Q}TOF machine. TCCA was procured from Avra company. *p*-Bromoacetophenone, 1-indanone, deoxybenzoin, salicyladehyde and thiourea were purchased from Sigma Aldrich and used as received.

General Procedure for the Synthesis of 2-Aminothiazole, Quinoxaline and Benzofuran Derivatives. In a representative reaction, the solid ketone (ca. 0.1 g, 0.5–0.8 mmol), 0.4 equivalent of nicely ground TCCA and 0.5 equivalent of *p*-TSA were introduced into a 5 mL stainless steel milling jar containing 6 stainless steel balls of diameter 3.0 mm. The reaction mixture was subsequently milled at a frequency of 20 Hz for 2-8 h at rt. After the formation of the intermediate(s) as determined by TLC analyses, thiourea/*N*-arylthiourea or 1,2-diamine/substituted-1,2-diamine or salicylaldehyde/3,5-dibromosalicylaldehyde (1.05 equiv) was introduced along with nicely powdered K_2CO_3 (1.5 equiv). The milling was continued for the durations mentioned in Schemes 1–4. For benzoylbenzofurans, *p*-TSA was additionally introduced and the milling was further continued. At the end of the reaction, the solid residue was taken up into ethyl acetate, whereby the organic material was extracted. The latter was dried over sodium sulfate, and the solvent removed under reduced pressure. The resultant solid residue was subjected to a short pad silica-gel chromatography to isolate the product(s) in each case.

Spectral Data of Products

2-(2,5-Dimethylphenyl)amino-4-(*p*-bromophenyl)thiazole (2f). Pale yellow solid; R_f 0.70 (5% EtOAc/petroleum ether); mp 128–130 °C; IR (KBr) cm^{-1} 3219, 3106, 2971, 1561, 1454; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.35 (s, 3H), 6.77 (s, 1H), 6.91 (d, J = 7.6 Hz, 1H), 7.12 (d, J = 7.6 Hz,

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2H), 7.44 (brs, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.4, 21.2, 102.2, 121.5, 121.5, 125.6, 126.4, 127.6, 130.9, 131.7, 133.5, 137.1, 138.3, 150.2, 166.7; ESI-MS$^+$: Exact mass calculated for $C_{17}H_{15}BrN_2S$ $[M]^+$: 358.0139, found: 358.0139.

2-(*p*-Chlorophenyl)amino-4,5-diphenylthiazole (2k). Colorless crystalline; R_f 0.48 (10% EtOAc/petroleum ether); mp 190–192 °C; IR (KBr) cm^{-1} 3236, 3090, 3061, 1595, 1551, 1492, 1430; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.17 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.25–7.30 (m, 8H), 7.49–7.52 (m, 2H), 8.18 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 119.6, 121.6, 127.5, 127.7, 127.8, 128.3, 128.6, 129.0, 129.3, 129.4, 132.1, 134.9, 138.9, 145.7, 162.4; ESI-MS$^+$: Exact mass calculated for $C_{21}H_{16}ClN_2S$ $[M+H]^+$: 363.0722, found: 363.0721.

4,5-Diphenyl-2-(*p*-tolyl)aminothiazole (2l). Colorless solid; R_f 0.50 (10% EtOAc/petroleum ether); mp 160–162 °C; IR (KBr) cm^{-1} 3125, 3059, 2927, 1597, 1556, 1514, 1435, 1299; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 2.33 (s, 3H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.19–7.22 (m, 2H), 7.24–7.31 (m, 8H), 7.50–7.52 (m, 2H), ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 20.8, 119.0, 127.3, 127.6, 128.2, 128.6, 128.9, 128.9, 129.4, 130.0, 132.4, 133.1, 135.1, 137.7, 145.6, 163.3*;* ESI-MS$^+$ Exact mass calculated for $C_{22}H_{19}N_2S$ $[M+H]^+$: 343.1268, found: 343.1268.

2-(2,5-Dimethylphenyl)amino-4,5-diphenylthiazole (2m). Colorless solid; R_f 0.55 (10% EtOAc/petroleum ether); mp 186–188 °C; IR (KBr) cm^{-1} 3153, 3051, 2921, 2890, 1561, 1493, 1432; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 2.29 (s, 3H), 2.35 (s, 3H), 6.90 (d, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.21–7.30 (m, 8H), 7.42 (s, 1H), 7.50–7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 17.4, 21.2, 121.3, 125.4, 126.4, 127.2, 127.6, 128.2, 128.5, 128.9, 129.4, 130.9, 132.5, 135.1, 137.0, 138.5, 145.7, 164.41; ESI-MS$^+$: Exact mass calculated for $C_{23}H_{21}N_2S$ $[M+H]^+$: 357.1425, found: 357.1428.

2-(*p*-Bromophenyl)amino-8*H*-indeno[1,2-*d*]thiazole (4c). Off-white solid; R_f 0.40 (10% EtOAc/petroleum ether); mp 188–190 °C; IR (KBr) cm^{-1} 3202, 3049, 2924, 1588, 1488; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 2H), 7.22 (td, *J* = 1.4, 7.3 Hz, 1H), 7.32–7.38 (m, 3H), 7.43–7.48 (m, 3H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.78 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.6, 115.1, 118.6, 119.7, 124.6, 124.9, 126.9, 132.3, 137.3, 139.3, 145.3, 156.9, 168.0; ESI-MS$^+$: Exact mass calculated for $C_{16}H_{11}BrN_2S$ $[M]^+$: 341.9826, found: 341.9821.

2-(*p*-Chlorophenyl)amino-8*H*-indeno[1,2-*d*]thiazole (4d). Off-white solid; R_f 0.40 (10% EtOAc/petroleum ether); mp 186–188 °C; IR (KBr) cm^{-1} 3205, 3053, 2930, 1594, 1491; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 2H), 7.22 (td, *J* = 1.4, 7.3 Hz, 1H), 7.30–7.36 (m, 3H), 7.39–7.43 (m, 2H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.52 (brs, 1H), 7.63 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.6, 118.6,

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119.5, 124.6, 124.7, 124.9, 126.9, 127.8, 129.4, 137.3, 138.8, 145.3, 156.8, 168.3; ESI-MS$^+$: Exact mass calculated for $C_{16}H_{11}ClN_2S$ $[M]^+$: 298.0331, found: 298.0333.

2-(*p*-Tolyl)amino-8*H*-indeno[1,2-*d*]thiazole (4e). Pale brown solid; R_f 0.35 (10% EtOAc/petroleum ether); mp 188–190 °C; IR (KBr) cm^{-1} 3207, 2914, 1596, 1562; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.73 (s, 2H), 7.16–7.22 (m, 3H), 7.29–7.34 (m, 3H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.68 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 32.6, 118.5, 119.3, 124.1, 124.5, 124.6, 126.9, 130.0, 133.2, 137.6, 145.4, 156.7, 169.9; ESI-MS$^+$: Exact mass calculated for $C_{17}H_{14}N_2S$ $[M]^+$: 278.0877, found: 278.0878.

2-(2,5-Dimethylphenyl)amino-8*H*-indeno[1,2-*d*]thiazole (4f). Colorless solid; R_f 0.35 (10% EtOAc/petroleum ether); mp 192–194 °C; IR (KBr) cm^{-1} 3155, 3053, 2916, 1584, 1559; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.36 (s, 3H), 3.72 (s, 2H), 6.93 (d, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.19 (td, *J* = 0.9, 7.6 Hz, 1H), 7.30–7.34 (m, 2H), 7.44–7.47 (m, 2H), 7.55 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 21.1, 32.6, 118.3, 122.3, 124.3, 124.5, 124.6, 125.8, 126.9, 127.1, 131.0, 137.0, 137.6, 138.2, 145.4, 156.7, 171.4; ESI-MS$^+$: Exact mass calculated for $C_{18}H_{16}N_2S$ $[M]^+$: 292.1034, found: 292.1032.

7/8-Methyl-11*H*-indeno[2,1-*b*]quinoxaline (6b+6b'). Pale yellow solid; R_f 0.40 (10% EtOAc/petroleum ether); isomers ratio (50:50); mp 146–148 °C; IR (KBr) cm^{-1} 3045, 2915, 1625, 1507; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (s, 3H), 4.13 (s, 2H), 7.53–7.60 (m, 3H), 7.65–7.68 (m, 1H), 7.86 (s, 0.5H), 7.95 (s, 0.5H), 7.98 (d, *J* = 8.7 Hz, 0.5H), 8.06 (d, *J* = 8.7 Hz, 0.5H), 8.22–8.26 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 35.9, 36.0, 122.4, 122.6, 125.8, 128.0, 128.0, 128.3, 128.4, 128.7, 130.8, 130.9, 131.0, 131.4, 138.2, 139.3, 139.6, 139.7, 140.4, 141.3, 142.1, 143.3, 143.5, 153.9, 154.5, 158.5, 159.4; ESI-MS$^+$: Exact mass calculated for $C_{16}H_{12}N_2$ $[M]^+$: 232.1000, found: 232.1009. (It should be noted that the ^{1}H and ^{13}C NMR spectral data are for an inseparable mixture. In ^{1}H NMR, some signals split up into two, while others merge. In ^{13}C NMR, several appear as closely spaced lines with some merged.)

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REFERENCES

1. (a) J. V. Metzger, *The Chemistry of Heterocyclic Compounds*: *Thiazole and Its Derivatives*, John Wiley & Sons, New York, 1979; (b) M. A. Metwally, E. Abdel-Latif, F. A. Amer and G. Kaupp, *J. Sulfur Chem*., 2004, **25**, 63; (c) F. Jiang, P. Zhou, J. Chen, Y. Wang, B. Cao and J. Yan, *Eur. Pat*., EP2682390A1, 2014.
2. (a) D. J. Brown, *The Chemistry of Heterocyclic Compounds Quinoxalines, Supplement II*, John Wiley & Sons, New Jersey, 2004; (b) K. L. Ameta, and A. Dandia, *Green Chemistry: Synthesis of Bioctive Heterocyles*, Springer, India, 2014.
3. M. G. Kadieva and T. Oganesyan, *Chem. Heterocycl. Compd*., 1997, **33**, 1245.
4. (a) H. Khanam and Shamsuzzaman, *Eur. J. Med. Chem.*, 2015, **97**, 483; (b) D. Das, P. Sikdar and M. Bairagi, *Eur. J. Med. Chem*., 2016, **109**, 89.
5. (a) N. Morita, K. Inoue and M. Takagi, *Agric. Biol. Chem.*, 1983, **47**, 1329; (b) M. C. Wilkes, P. B. Lavrik and J. Greenplate, *Synthesis and Chemistry of Agrochemicals III: N-Benzoyl-N-alkyl-2-aminothiazole Proinsecticides*, ACS Symposium Series, Washington, 2009; (c) S. T. Lee, T. Z. Davis, D. R. Gardner, B. L. Stegelmeier and T. J. Evans, *J. Agric. Food Chem.,* 2009, **57**, 5639;
6. (a) H. M. Refaat, A. A. Moneer and O. M. Khalil, *Arch. Pharm. Res*., 2004, **27**, 1093; (b) M. Koca, S. Servi, C. Kirilmis, M. Ahmedzade, C. Kazaz, B. Ozbek and G. Otuk, *Eur. J. Med. Chem*., 2005, **40**, 1351; (c) S. Annadurai, R. Martinez, D. J. Canney, T. Eidem, P. M. Dunman and M. Abou-Gharbi, *Bioorg. Med. Chem. Lett*., 2012, **22**, 7719; (d) H. Asha, R. P. Mahadeo, K. R. Chethana, C. Karam, M. S. Amelia and S. K. Rangappa, *RSC Adv*., 2015, **5**, 96809.
7. (a) S. A. Galal, A. S. A. El-All, M. M. Abdallah and H. I. El-Diwani, *Bioorg. Med. Chem. Lett*., 2009, **19**, 2420; (b) M. O. Shibinskaya, S. A. Lyakhov, A. V. Mazepa, S. A. Andronati, A. V. Turov, N. M. Zholobak and N. Y. Spivak, *Eur. J. Med. Chem*., 2010, **45**, 1237; (c) M. Mori, Nucci, A.; M. C. D. Lang, N. Humbert, C. Boudier, F. Debaene, S. Sanglier-Cianferani, M. Catala, P. Schult-Dietrich, U. Dietrich, C. Tisne, Y. Mely and M. Botta, *ACS Chem. Biol*., 2014, **9**, 1950.
8. (a) R. N. Misra, H. Xiao, K. S. Kim, S. Lu, W. -C. Han, S. A. Barbosa, J. T. Hunt, D. B. Rawlins, W. Shan, S. Z. Ahmed, L. Qian, B. -C. Chen, R. Zhao, M. S. Bednarz, K. A. Kellar, J. G. Mulheron, R. Batorsky, U. Roongta, A. Kamath, P. Marathe, S. A. Ranadive, J. S. Sack, J. S. Tokarski, N. P. Pavletich, F. Y. F. Lee, K. R. Webster and S. D. Kimball, *J. Med. Chem.,* 2004, **47**, 1719; (b) P. Corona, A. Carta, M. Loriga, G. Vitale and G. Paglietti, *Eur. J. Med. Chem*., 2009, **44**, 1579.
9. (a) K. M. Dawood, H. Abdel-Gawad, E. A. Rageb, M. Ellitheyc and H. A. Mohamed, *Bioorg. Med. Chem*., 2006, **14**, 3672; (b) O. Kouatly, A. Geronikaki, C. Kamoutsis, D. Hadjipavlou-Litina and P.

View Article Online
DOI: 10.1039/C6OB00351F

Eleftheriou, *Eur. J. Med. Chem*., 2009, **44**, 1198; (c) A. Burguete, E. Pontiki, D. Hadjipavlou-Litina, S. Ancizu, R. Villar, B. Solano, E. Moreno, E. Torres, S. Perez, I. Aldana and A. Monge, *Chem. Biol. Drug. Des*., 2011, **77**, 255.

10. (a) P. Jimonet, F. Audiau, M. Barreau; J.-C. Blanchard, A. Boireau, Y. Bour, M. -A. Coleno, A. Doble, G. Doerflinger, C. D. Huu, M. -H. Donat, J. M. Duchesne, P. Ganil, C. Gueremy, E. Honore, B. Just, R. Kerphirique, S. Gontier, P. Hubert, P. M. Laduron, J. L. Blevec, M. Meunier, J. -M. Miquet, C. Nemecek, M. Pasquet, O. Piot, J. Pratt, J. Rataud, M. Reibaud, J. -M. Stutzmann and S. Mignani, *J. Med. Chem.,* 1999, **42**, 2828; (b) L. J. Katz, S. T. Simmons and E. R. Craven. *Curr. Med. Res. Opin*., 2007, **23**, 2971; (c) M. M. Yardley, M. M. Mirbaba and L. A. Ray, *CNS Drugs,* 2015, **29**, 833.
11. (a) K. R. J. Thomas, J. T. Lin, Y. -T. Tao and C. -H. Chuen, *Chem. Mater*., 2002, **14**, 2796; (b) K. R. J. Thomas, M. Velusamy, J. T. Lin, C. H. Chuen and Y. -T. Tao, *Chem. Mater*., 2005, **17**, 1860; (c) S. Ando, R. Murakami, J. -I. Nishida, H. Tada, Y. Inoue, S. Tokito and Y. Yamashita, *J. Am. Chem. Soc.,* 2005, **127**, 14996; (d) S. K. Lee, J. M. Cho, Y. Goo, W. S. Shin, J. -C. Lee, W. -H. Lee, I. -N. Kang, H. -K. Shim and S. -J. Moon, *Chem. Commun.,* 2011, **47**, 1791; (e) Y. Lin, H. Fan, Y. Li and X. Zhan, *Adv. Mater.,* 2012*,* **24**, 3087.
12. (a) H. R. Maradiya and V. S. Patel, *Chem. Heterocycl. Compd*., 2003, **39**, 357; (b) R. W. Sabnis**,** *Handbook of Biological Dyes and Stains: Synthesis and Industrial Applications*, John Wiley & Sons, New Jersey, 2010; (c) D. W. Chang, H. J. Lee, J. H. Kim, S. Y. Park, S.-M. Park, L. Dai and J. -B. Baek, *Org. Lett*., 2011, **13**, 3880; (d) A. P. Chafin, M. C. Davis, W. W. Lai, G. A. Lindsay, D. H. Park and W. N. Herman, *Opt. Mater*., 2011, **33**, 1307.
13. A. W. Erian, S. M. Sherif and H. M. Gaber, *Molecules,* 2003, **8**, 793.
14. (a) M. D. Chordia, L. J. Murphree, T. L. Macdonald, J. Linden and R. A. Olsson, *Bioorg. Med. Chem. Lett*., 2002, **12**, 1563; (b) A. Goblyos, S. Santiago, N. D. Pietra, T. Mulder-Krieger, J. F. D. Kunzel, J. Brussee and A. P. IJzerman, *Bioorg. Med. Chem*., 2005, **13**, 2079; (c) Y.-P. Zhu, J. -J. Yuan, Q. Zhao, M. Lian, Q. -H. Gao, M. -C. Liu, Y. Yang, A. -X. Wu, *Tetrahedron,* 2012, **68**, 173; (d) S. Koppireddi, J. Komsani, S. Avula, S. Pombala, S. Vasamsetti, S. Kotamraju and R. Yadla, *Eur. J. Med. Chem*., 2013, **66**, 305; (e) J. -R. Li, D. -D. Li, R. -R. Wang, J. Sun, J. -J. Dong, Q. -R. Du, F. Fang, W. -M. Zhang and H. -L. Zhu, *Eur. J. Med. Chem*., 2014, **75**, 438.
15. T. J. Donohoe, M. A. Kabeshov, A. H. Rathi and I. E. D. Smith, *Org. Biomol. Chem*., 2012, **10**, 1093.
16. (a) M. Lian, Q. Li, Y. Zhu, G. Yin and A. Wu, *Tetrahedron,* 2012, **68**, 9598; (b) B. Tanwar, P. Purohit, B. N. Raju, D. Kumar, D. N. Kommi and A. K. Chakraborti, *RSC Adv*., 2015, **5**, 11873.
17. Y. Shang, C. Wang, X. He, K. Ju, M. Zhang, S. Yu and J. Wu, *Tetrahedron,* 2010, **66**, 9629.

View Article Online
DOI: 10.1039/C6OB00351F

18. U. Tilstam and H. Weinmann, *Org. Process Res. Dev.,* 2002, **6**, 384.

19. A. K. Mishra, H. Nagarajaiah and J. N. Moorthy, *Eur. J. Org. Chem.*, 2015, 2733.

20. J. D. Bonk, D. T. Amos and S. J. Olson, *Synth. Commun.*, 2007, **37**, 2039.

21. (a) A. Stolle, T. Szuppa, S. E. S. Leonhardt and B. Ondruschka, *Chem. Soc. Rev.,* 2011, **40**, 2317–2329; (b) G. –W. Wang, *Chem. Soc. Rev.*, 2013, **42**, 7668.

22. (a) W. C. Shearouse, C. M. Korte and J. Mack, *Green Chem.,* 2011, **13**, 598; (b) Z. Zhang, H. -H. Wu and Y. -J. Tan, *RSC Adv.*, 2013, **3**, 16940; (c) N. Mukherjee, T. Chatterjee and B. C. Ranu, *J. Org. Chem.*, 2013, **78**, 11110; (d) Y. -J. Tan, Z. Zhang, F. -J. Wang, H. -H. Wu and Q. -H. Li, *RSC Adv.*, 2014, **4**, 35635.