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PAPER

Unexpected reactivity of diaryl α-diketones with thiazolium carbenes: discovery of a novel multicomponent reaction for the facile synthesis of 1,4-thiazin-3-ones†

Valerio Bertolasi, Olga Bortolini, Adelaide Donvito, Giancarlo Fantin,* Marco Fogagnolo, Pier Paolo Giovannini, Alessandro Massi* and Salvatore Pacifico

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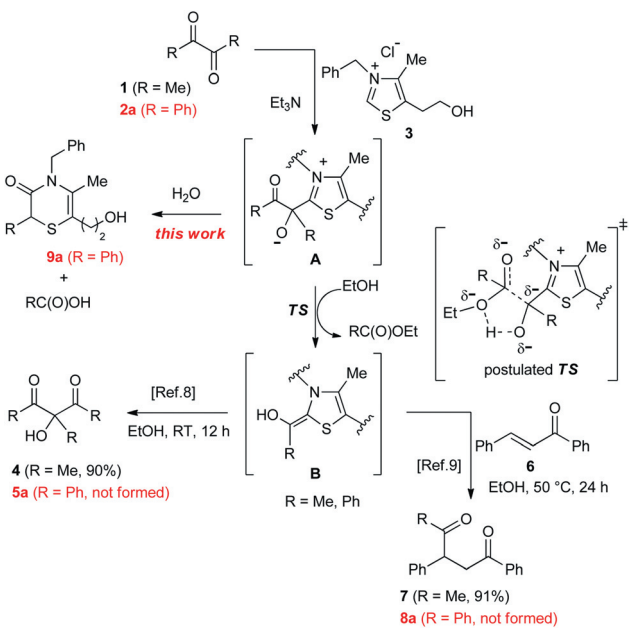
Diaryl α-diketones do not undergo polarity reversal in the presence of (benzo)thiazolium carbenes but are engaged in a novel multicomponent reaction with water to efficiently give medicinally relevant 1,4-thiazin-3-one heterocycles. Three different sets of conditions have been optimized to furnish the title compounds in fair to excellent yields depending on the electronic properties of α-diketone aromatic substituents and thiazolium or benzothiazolium substrate. A plausible reaction mechanism is also proposed based on the isolation and characterization of the postulated key intermediate and isotopic labeling experiments.

In recent years, *N*-heterocyclic carbenes (NHCs) have attracted considerable interest due to their unique features (amphiphilicity, moderate nucleophilicity, or strong basicity),[1] which allow them to be used as ligands for organometallic catalysis,[2] as reagents in the synthesis of heterocycles,[3] and as efficient organocatalysts in *umpolung* transformations.[4] In the latter sub-area of research many efforts have been devoted to the realization of highly stereoselective versions of the classical benzoin and Stetter reactions through optimal pre-catalyst design,[4a,c–e] to the discovery of new transformations[4b,f] (including domino processes),[1b] and to the *umpolung* of electrophiles alternative to aldehydes and pyruvates, mainly acylsilanes[4f,5] and Michael acceptors.[6] In this regard, our group has recently demonstrated the capability of linear and cyclic dialkyl α-diketones to undergo polarity reversal under thiazolium carbene catalysis in benzoin-type[7,8] and Stetter reactions,[9] and thus act as a novel class of acyl anion precursors (Scheme 1). Crucial for the successful generation of the reactive Breslow intermediate **B** from dialkyl 1,2-diones of type **1** is the cleavage of the relatively weak 1,2 C–C bond that we postulated to occur through an alkoxide-assisted nucleophilic attack of the amphiprotic solvent EtOH to the adduct **A**.[9] As part of our research on the reactivity of 1,2-dicarbonyls with NHCs and thiamine-dependent enzymes, we present herein the results of a parallel study with diaryl 1,2-diones **2** (benzils) showing that



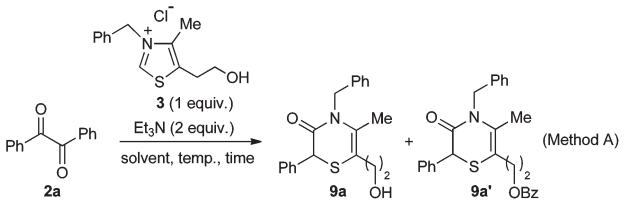
Scheme 1 Reactions of dialkyl and diaryl α-diketones promoted by thiazolium-derived carbenes.

they cannot serve as surrogates of aromatic aldehydes by thiazolin-2-ylidene catalysis. This investigation, however, culminated with the identification and optimization of a novel multicomponent reaction (MCR), in which benzils are intercepted by equimolar amounts of a thiazolium/benzothiazolium carbene and water to generate 4*H*-1,4-thiazin-3-one derivatives of type **9** in a straightforward manner (one-pot procedures). Notably, these heterocyclic systems are endowed with a broad range of

Dipartimento di Chimica, Laboratorio di Chimica Organica, Università di Ferrara, Via *L. Borsari 46, I-44121 Ferrara, Italy.*
E-mail: alessandro.massi@unife.it

†Electronic supplementary information (ESI) available: copies of ^{1}H and ^{13}C NMR spectra for new compounds and HRMS (ESI/Q-TOF) spectrum of ^{18}O-labelled **9a**. CCDC 875932. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25928a

Table 1 Discovery of the novel 3CR of benzil **2a**, thiazolium salt **3**, and water and its optimization *via* the one-step thermal procedure (Method A)[a]

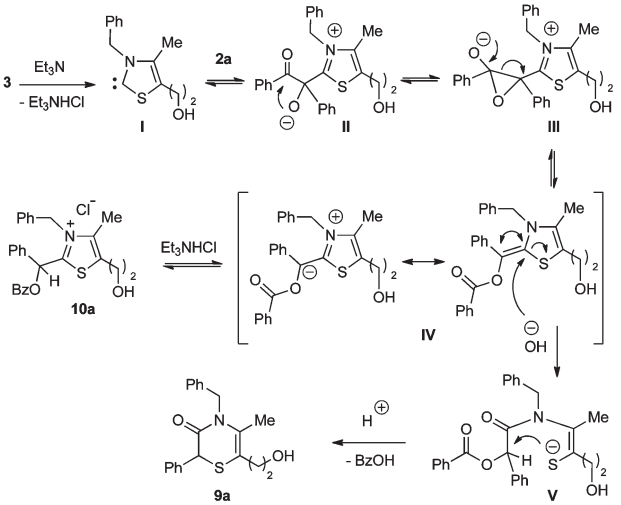


Entry	Solv.	Temp. (°C)	Time (h)	**9a** + **9a′**[b]	**9a′**[c]
1[d]	EtOH	25	24	—	—
2	EtOH	50	24	8 + —	—
3	DMF[e]	50	16	52 + 5	47
4	DMF[e]	70	16	58 + 5	50
5	DMF[e]	80	16	64 + 8	63
6	DMF[f]	80	16	47 + 8	42
7	DMF[g]	80	16	58 + 10	58
8	DMF[g]	25	96	37 + 15	40
9[h]	DMF	100	2	63 + —	53
10[h]	DMF	100	3	40 + 5	32

[a] Reactions performed with 1.00 mmol of **2a** (0.5 M). [b] Determined by ^{1}H NMR analysis of the crude reaction mixture (mol%). [c] Isolated yield after treatment of crude reaction mixture with BzCl and pyridine (see Experimental section). [d] Reaction performed with 20 mol% of **3**. A similar result was obtained in PEG_{400}. [e] Wet DMF (water content *ca.* 10–20%). [f] Anhyd. DMF + 5 equiv. of H_2O. [g] Anhyd. DMF + 10 equiv. of H_2O. [h] Microwave-assisted reaction performed with a single-mode cavity dedicated reactor (Biotage Initiator).

pharmacological activities,[10] and are typically prepared by multi-step synthetic sequences.[11] Moreover, since the first report of Nair and co-workers on carbene-triggered MCRs,[12] the utility of this class of reactions has been amply demonstrated by the synthesis of a number of heterocyclic scaffolds only accessible with difficulty by other procedures.[13] Nevertheless, as most of the known NHC-based MCRs involve an activated alkyne and a carbonyl compound or ketene as NHC reaction partners, the relative studies are limited to the production of furan derivatives.[12,13b,d,f–j,q,r]

As anticipated, our investigation on the conceptually novel 3CR of diaryl 1,2-diones, thiazolium salts, and water commenced with the observation that benzil **2a** was not reactive under the conditions previously optimized for the homo-coupling of biacetyl **1** (Scheme 1 and Table 1, entry 1). Thus, it was envisaged that both reaction temperature and pre-catalyst **3** loading could play a significant role in the generation of the acyl anion from **2a**. Surprisingly, an experiment (entry 2) conducted in EtOH at 50 °C with equimolar **2a**/**3** and in the presence of Et_3N (2 equiv.) produced the 2,3-dihydro-4*H*-1,4-thiazin-3-one **9a** (8%) and benzoic acid (BzOH) as the sole isolable reaction products (**2a** conversion: 15%).[14] The realization that compound **9a** was the 1/1/1 adduct of **2a**, water, and thiazolium **3**-derived carbene, as well as the recognition of the pharmaceutical relevance of the 1,4-thiazine scaffold,[10] prompted us to further investigate the synthetic potential of this hitherto unreported 3CR. Hence, on the basis of a tentative mechanistic hypothesis (see below), the effect on reaction outcome of the change from an amphiprotic to a polar aprotic solvent such as DMF was first evaluated. Indeed, this choice proved to be successful furnishing

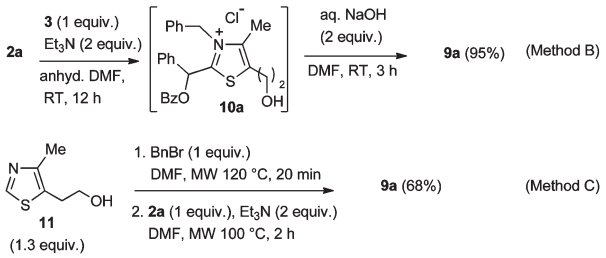


Scheme 2 Proposed reaction pathway for the 3CR of thiazolium carbenes, diaryl α-diketones, and water.

a much higher yield (52%) of **9a**, which was formed together with its benzoyl derivative **9a′** (5%; entry 3).[14] Further experimentation was next carried out to determine the optimal reaction temperature (T = 80 °C, entries 4–5), and to better establish the influence of water amount on reaction efficiency (entries 6–8). These latter experiments were conducted in anhydrous DMF under inert atmosphere with increasing quantities of added water (up to 10 equiv.), but no significant improvements were observed in comparison with the run performed in wet DMF (entry 5). Aiming at decreasing the reaction time of the optimized one-step thermal procedure (Method A; entry 5), the use of microwave (MW) dielectric heating was finally considered (entries 9–10). Thus, the better compromise between product yield (63%) and selectivity was found by irradiating the reaction mixture at 100 °C for 2 h (entry 9).[14]

A mechanistic rationalization for the observed reactivity of diaryl α-diketones is proposed as shown in Scheme 2. Thus, the *in situ* generated thiazolin-2-ylidene **I** initially attacks benzil **2a** to give the alkoxide **II**, which then rearranges to form the zwitterion **IV** through the epoxide intermediate **III**. In the basic reaction medium, the ring opening of **III** by nucleophilic addition of the hydroxyl anion produces a reactive thiolate **V**, which subsequently undergoes cyclization to produce the 4*H*-1,4-thiazin-3-one ring by elimination of benzoate. Notably, the involvement of epoxide intermediates in the nucleophilic addition of carbenes to 1,2-diones has precedent in studies from Schowen[15] and Nair[13i,16] groups. Also, the NHC-promoted thiazolium ring expansion has been previously reported by Takamizawa,[17] Ma[13f,h] and their co-workers. Thus, given the above reasoning, it can be speculated that the effective stabilization of electron density at the exocyclic C1 atom of **IV** by the aromatic and benzoyl groups is responsible for the preferential formation of **IV** over the Breslow intermediate **B** (Scheme 1, R = Ph).

An experimental result in support of our mechanistic hypothesis was the isolation and characterization (NMR and MS) of thiazolium salt **10a** bearing a benzoyl group at the *exo*-C1 position. This salt was quantitatively recovered from an experiment conducted at room temperature under strictly anhydrous



Scheme 3 One-pot two-step 3CR (Method B) and one-pot two-step 4CR (Method C) leading to 1,4-thiazin-3-one **9a**.

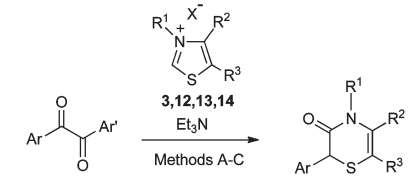
conditions with equimolar **2a/3** in DMF as the solvent (Scheme 3). This outcome prompted us to set up an alternative procedure for the model 3CR, which consisted in simply adding 10% aqueous NaOH (2 equiv.) to the solution of crude **10a** (Method B). This novel protocol furnished the thiazin-3-one **9a** under milder conditions (RT) and in almost quantitative yield.[14] Significantly, addition of $H_2{}^{18}O$ (10 equiv.) to the intermediate **10a** (anhydr. DMF, RT, 72 h) smoothly led to ^{18}O-labelled **9a** (see Table 2, entry 1),[18] thus providing further evidence for the proposed MCR mechanism.

The 4CR of thiazole **11**, BnBr, benzil **2a**, and water was finally considered (Method C, Scheme 3). A two-step sequence entailing generation of the thiazolium salt **3** and subsequent completion of the Et_3N-promoted MCR was made necessary because of the incompatibility in the same pot and basic medium of the alkylating agent and the 1,2-dione substrate. The whole one-pot procedure, however, was accelerated by the use of MW irradiation and gave **9a** in 68% yield.[14]

With three sets of optimized conditions in hand (Methods A–C), the generality of the MCR was next explored (Tables 2 and 3). Utilization of thiazolium salts **12–14** with different *N*-substituents and groups at 4- and 5-positions had no significant impact on reaction yields (entries 3–5). By contrast, and in full agreement with our mechanistic hypothesis, diketone **2b** with an electron-withdrawing group (4-Br) on the aromatic ring performed much better (entries 6–7) than its counterpart **2c** having an electron-donating aromatic group (4-Me). In particular, thermal procedures (Methods A and C) with **2c** were quite sluggish furnishing low yields of thiazin-3-ones **16c** and **17c** (entries 8–9). The unfavorable effect of aromatic electron-withdrawing groups on reaction efficiency was further confirmed by an experiment conducted with the unsymmetrical diaryl diketone **2d** that yielded (Method B) the thiazin-3-one **16b** as the sole reaction product (entry 10). To our satisfaction, however, compound **16b** gave crystals suitable for X-ray analysis,[18] thus providing an unambiguous structural assignment of thiazin-3-ones prepared (Fig. 1).

The reactivity of benzothiazolium carbenes was also investigated (Table 3). When *N*-benzyl benzothiazolium salt **18** was engaged in the MCR with benzyl **2a**, no desired benzothiazin-3-one product **20** was obtained (entry 1), while significant amounts (40–65%) of the by-product **23** were recovered. This was formed under thermal conditions (Methods A and C) by [1,3] sigmatropic rearrangement of the *in situ* generated benzothiazolin-2-ylidene dimer (not shown) through formation of the stable benzyl radical.[19] Thus, it was envisaged that replacement

Table 2 Scope of the MCR with diaryl α-diketones **2a–d** and thiazolium salts **3**, **12–14**[a]



2a Ar = Ar'= Ph
2b Ar = Ar' = 4-BrPh
2c Ar = Ar' = 4-MePh
2d Ar = 4-BrPh; Ar' = 4-MePh

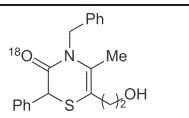
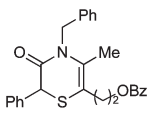
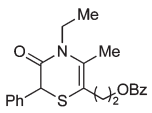
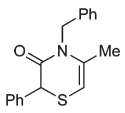
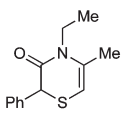
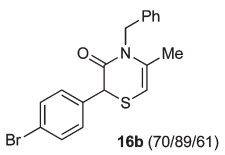
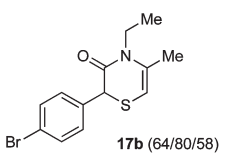
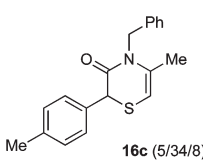
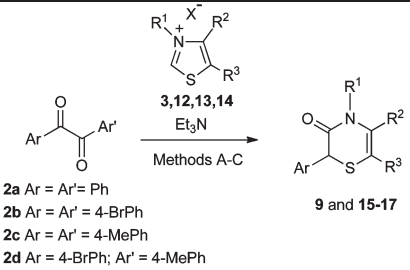
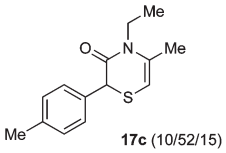
Entry	Diketone	Thiazolium salts (R^1, R^2, R^3)	Product[b] (%)
1[c]	**2a**	**3** (Bn, Me, –$(CH_2)_2$OH)	 **^{18}O-labelled 9a** (- /90/ -)[d]
2	**2a**	**3** (Bn, Me, –$(CH_2)_2$OH)	 **9a'** (63/88/53)
3	**2a**	**12** (Et, Me, –$(CH_2)_2$OH)	 **15a'** (60/82/55)
4	**2a**	**13** (Bn, Me, H)	 **16a** (61/85/56)
5	**2a**	**14** (Et, Me, H)	 **17a** (57/80/51)
6	**2b**	**13** (Bn, Me, H)	 **16b** (70/89/61)
7	**2b**	**14** (Et, Me, H)	 **17b** (64/80/58)
8	**2c**	**13** (Bn, Me, H)	 **16c** (5/34/8)

Table 2 *(Contd.)*



Entry	Diketone	Thiazolium salts (R^1, R^2, R^3)	Product[b] (%)
9	**2c**	**14** (Et, Me, H)	 **17c** (10/52/15)
10	**2d**	**13** (Bn, Me, H)	**16b** (–/45/–)

[a] Reactions performed with 1.00 mmol of diketone (0.5 M) and 1.00 mmol of thiazolium salt. [b] Isolated yields (Method A/Method B/Method C). In the case of derivatives **9a′** and **15a′** the reported values refer to the isolated yields after treatment of the crude MCR mixture with BzCl and pyridine (see Experimental section). [c] Reaction performed with $H_2{}^{18}O$. [d] Determined by ^1H NMR (isolated yield: 45%).

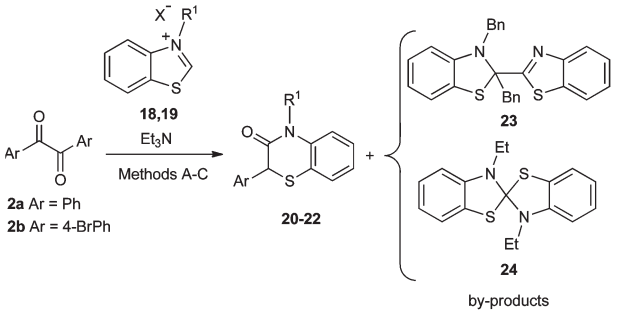
of the *N*-Bn substituent on benzothiazolium salt could be crucial for succeeding in the planned MCR with benzils **2a,b**. Quite gratifyingly, although production of the spiro-benzothiazole side-product **24**[20] could not be suppressed (30–40%), it was possible to isolate the target benzothiazin-3-ones **21–22** in acceptable yields (40–45%) by the MW-assisted Method C (entries 2 and 3).

In conclusion, the unexpected reactivity of diaryl α-diketones with (benzo)thiazolium carbenes has been exploited to optimize a novel multicomponent reaction leading to pharmaceutically relevant (benzo)thiazin-3-one derivatives. Research on the *umpolung* reactivity of diaryl 1,2-diones by different NHC organocatalysts and the set-up of a diastereoselective version of the disclosed MCR are currently underway.

Experimental

Reactions were monitored by TLC on silica gel 60 F254 with detection by charring with phosphomolybdic acid. Flash column chromatography was performed on silica gel 60 (230–400 mesh). ^1H (400 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in $CDCl_3$ solutions at room temperature. Peak assignments were aided by ^1H–^1H COSY and gradient-HMQC/HMBC experiments. ESI-MS analyses were performed in positive ion mode with samples dissolved in 10 mM solution of ammonium formate in 1 : 1 MeCN–H_2O. For accurate mass measurements, the compounds were analyzed in positive ion mode by Agilent 6520 HPLC-Chip Q/TOF-MS (nanospray) using a quadrupole, a hexapole, and a time-of-flight unit to produce spectra. The capillary source voltage was set at 1700 V; the gas temperature and drying gas were kept at 350 °C and

Table 3 Scope of the MCR with diaryl α-diketones **2a,b** and benzothiazolium salts **18–19**[a]



Entry	Diketone	Thiazolium salts (R^1, R^2, R^3)	Product[b] (%)
1	**2a**	**18** (R^1 = Bn)	**20** (-/ - /-)
2	**2a**	**19** (R^1 = Et)	**21** (20/ - /42)
3	**2b**	**19** (R^1 = Et)	**22** (18/ - /45)

[a] Reactions performed with 1.00 mmol of diketone (0.5 M) and 3.00 mmol of benzothiazolium salt. [b] Isolated yields (Method A/Method B/Method C).

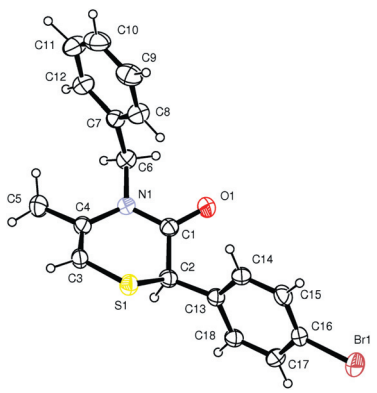


Fig. 1 ORTEP view of **16b** showing the thermal ellipsoids at 30% level of probability.

5 L min^{-1}, respectively. The MS analyzer was externally calibrated with ESI-L low concentration tuning mix from *m/z* 118 to 2700 to yield accuracy below 5 ppm. Accurate mass data were collected by directly infusing samples in 40/60 H_2O/ACN 0.1% TFA into the system at a flow rate of 0.4 μL min^{-1}. Elemental analyses were performed with FLASH 2000 Series CHNS/O

analyzer (ThermoFisher Scientific). Microwave-assisted reactions were carried out using a single-mode cavity dedicated reactor (Biotage Initiator™). Reactions were performed with temperature-controlled programs in glass vials (0.5–2 or 2–5 mL depending on the scale) sealed with a Teflon septum. Temperatures were measured externally by an IR sensor. The reaction time was counted when the reaction mixture reached the stated temperature. Pressure was measured by a non-invasive sensor integrated into the cavity lid. α-Diketones **2a–c**, thiazolium salts **3**, **12**, and (benzo)thiazole precursors of (benzo)thiazolium salts **3**, **12–14**, **18**, and **19** are commercially available (Sigma-Aldrich). 1,4-Thiazin-3-one **9a′**[17] and benzothiazoline derivative **23**[19] are known compounds. Thiazolium salts **13**, **14**, and benzothiazolium salts **18**, **19** were prepared according to known procedures.[21,22] Unsymmetrical 4-bromo-4′-methylbenzil was prepared as described.[23]

Optimized one-pot one-step procedure (Method A) for the three-component synthesis of 1,4-thiazin-3-one derivatives 9, 15, 16, 17, 21, and 22

To a stirred solution of thiazolium salt (1.00 mmol) or benzothiazolium salt (3.00 mmol) and α-diketone (1.00 mmol) in DMF (2 mL), was added Et_3N (279 μL, 2.00 mmol) in one portion. The mixture was warmed to 80 °C, stirred at that temperature for 14 h, and then cooled to room temperature and concentrated. The resulting residue was diluted with AcOEt (150 mL) and then washed with H_2O (2 × 20 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with the appropriate elution system to give the corresponding 1,4-thiazin-3-one derivative (Tables 2 and 3). When 4,4′-dibromo benzil **2b** was used, the addition to the reaction mixture of a few drops of 1-methyl-2-pyrrolidinone (NMP) was required to obtain a fully homogeneous solution. The crude MCR mixtures containing compounds **9a** and **15a** were dissolved in pyridine (2 mL) and treated with benzoyl chloride (232 μL, 2.00 mmol) for 14 h to give the corresponding benzoylated derivatives **9a′** and **15a′**, which were purified by column chromatography.

4-Benzyl-6-(2-hydroxyethyl)-5-methyl-2-phenyl-2,3-dihydro-4*H*-1,4-thiazin-3-one (9a). Column chromatography with 3 : 1 cyclohexane–AcOEt of the crude MCR mixture afforded **9a** (142 mg, 42%) as a white amorphous solid. IR (film) ν_{max}: 1655, 1270, 1115, 712, 695 cm^{-1}; ^1H NMR: δ = 7.37–7.20 (m, 10 H, Ar), 5.56 and 4.72 (2 d, 2 H, J = 16.0 Hz, PhCH_2), 4.66 (s, 1 H, H-2), 3.47–3.38 and 3.60–3.28 (2 m, 2 H, 2 H-2′), 2.52 (ddd, 1 H, $J_{1'a,2'a}$ = 5.0 Hz, $J_{1'a,2'b}$ = 8.5 Hz, $J_{1'a,1'b}$ = 14.5 Hz, H-1′a), 2.04 (ddd, 1 H, $J_{1'b,2'a}$ = 4.0 Hz, $J_{1'b,2'b}$ = 4.5 Hz, $J_{1'a,1'b}$ = 14.5 Hz, H-1′b), 1.91 (s, 3 H, CH_3). ^{13}C NMR: δ = 164.8, 137.0, 135.7, 132.8, 128.6, 128.5, 128.4, 128.2, 128.1, 127.4, 127.3, 127.2, 126.5, 126.5, 111.6, 61.0, 46.7, 45.8, 35.7, 15.8. ESI-MS (339.1): 362.5 (M + Na^+). Found: C, 70.77; N, 4.13; S, 9.45; H, 6.24. $C_{20}H_{21}NO_2S$ requires C, 70.89; N, 4.01; S, 9.71; H, 6.45%.

2-(4-Benzyl-5-methyl-3-oxo-2-phenyl-2,3-dihydro-4*H*-1,4-thiazin-6-yl)ethyl benzoate (9a′). Column chromatography with 9 : 1 cyclohexane–AcOEt afforded **9a′**[17] (279 mg, 63%) as a white amorphous solid. IR (film) ν_{max}: 1715, 1656, 1269, 1111, 709, 694 cm^{-1}; ^1H NMR: δ = 7.86–7.80, 7.60–7.50, and 7.40–7.10 (3 m, 15 H, Ar), 5.39 and 4.85 (2 d, 2 H, J = 16.0 Hz, PhCH_2), 4.62 (s, 1 H, H-2), 4.22 (ddd, 1 H, $J_{1'b,2'a}$ = 5.5 Hz, $J_{1'a,2'a}$ = 6.0 Hz, $J_{2'a,2'b}$ = 12.5 Hz, H-2′a), 4.04 (ddd, 1 H, $J_{1'b,2'b}$ = 6.0 Hz, $J_{1'a,2'b}$ = 7.5 Hz, $J_{2'a,2'b}$ = 12.5 Hz, H-2′b), 2.67 (ddd, 1 H, $J_{1'a,2'a}$ = 6.0 Hz, $J_{1'b,2'b}$ = 7.5 Hz, $J_{1'a,1'b}$ = 15.0 Hz, H-1′a), 2.45 (ddd, 1 H, $J_{1'b,2'a}$ = 5.5 Hz, $J_{1'b,2'b}$ = 6.0 Hz, $J_{1'a,1'b}$ = 15.0 Hz, H-1′b), 1.83 (s, 3 H, CH_3). ^{13}C NMR: δ = 166.3, 165.0, 137.0, 135.0, 132.9, 132.3, 129.9, 129.5–126.4 (15 C), 111.4, 62.9, 47.0, 45.9, 32.3, 15.8. ESI-MS (443.1): 466.8 (M + Na^+). Found: C, 73.11; N, 3.16; S, 7.23; H, 5.68. $C_{27}H_{25}NO_3S$ requires 73.34; N, 3.35; S, 7.03; H, 5.42%.

4-Ethyl-6-(2-hydroxyethyl)-5-methyl-2-phenyl-2,3-dihydro-4*H*-1,4-thiazin-3-one (15a). Column chromatography with 3 : 1 cyclohexane–AcOEt of the crude MCR afforded **15a** (111 mg, 40%) as a white amorphous solid. IR (film) ν_{max}: 1657, 1270, 1112, 710, 690 cm^{-1}; ^1H NMR: δ = 7.37–7.25 (m, 5 H, Ar), 4.53 (s, 1 H, H-2), 4.06 (dq, 1 H, $J_{1'a,Me}$ = 7.0 Hz, $J_{1'a,1'b}$ = 14.5 Hz, H-1′a), 3.71 (dq, 1 H, $J_{1'b,Me}$ = 7.0 Hz, $J_{1'a,1'b}$ = 14.5 Hz, H-1′b), 3.50–3.40 (m, 1 H, H-2″a), 3.39–3.28 (m, 1 H, H-2″b), 2.62 (ddd, 1 H, $J_{1'a,2''a}$ = 5.5 Hz, $J_{1''a,2''b}$ = 9.5 Hz, $J_{1''a,1''b}$ = 15.0 Hz, H-1″a), 2.04 (ddd, 1 H, $J_{1''b,2''a}$ = 4.5 Hz, $J_{1''b,2''b}$ = 5.0 Hz, $J_{1''a,1''b}$ = 15.0 Hz, H-1″b), 2.02 (s, 3 H, CH_3), 1.24 (t, 3 H, J = 7.0 Hz, CH_3), 0.36 (bdd, $J_{2''a,OH}$ = 5.2 Hz, $J_{2b'',OH}$ = 8.1 Hz, OH). ^{13}C NMR: δ = 163.9, 136.1, 132.6, 128.5, 128.4, 128.1, 128.0, 127.2, 110.4, 61.2, 46.5, 38.3, 35.7, 15.5, 13.8. ESI-MS (277.1): 278.8 (M + H^+). Found: C, 64.95; N, 5.05; S, 11.56; H, 6.90. $C_{15}H_{19}NO_2S$ requires C, 64.77; N, 5.32; S, 11.39; H, 6.75%.

2-(4-Ethyl-5-methyl-3-oxo-2-phenyl-2,3-dihydro-4*H*-1,4-thiazin-6-yl)ethyl benzoate (15a′). Column chromatography with 9 : 1 cyclohexane–AcOEt afforded **15a′** (229 mg, 60%) as a yellow amorphous solid. IR (film) ν_{max}: 1715, 1655, 1269, 1111, 709, 694 cm^{-1}; ^1H NMR: δ = 7.90–7.80,7.60–7.50, and 7.40–7.10 (3 m, 10 H, Ar), 4.49 (s, 1 H, H-2), 4.21 (ddd, 1 H, $J_{1''b,2''a}$ = 5.5 Hz, $J_{1''a,2''a}$ = 6.5 Hz, $J_{2''a,2''b}$ = 12.5 Hz, H-2″a), 4.08–4.02 (m, 1 H, H-2″b), 3.97 (dq, 1 H, $J_{1'a,Me}$ = 7.0 Hz, $J_{1'a,1'b}$ = 15.0 Hz, H-1′a), 3.74 (dq, 1 H, $J_{1'b,Me}$ = 7.0 Hz, $J_{1'a,1'b}$ = 15.0 Hz, H-1′b), 2.74 (ddd, 1 H, $J_{1''a,2''a}$ = 6.5 Hz, $J_{1''a,2''b}$ = 7.5 Hz, $J_{1''a,1''b}$ = 15.0 Hz, H-1″a), 2.46 (ddd, 1 H, $J_{1''b,2''a}$ = 5.5 Hz, $J_{1''b,2''b}$ = 5.8 Hz, $J_{1''b,1''a}$ = 15.0 Hz, H-1″b), 2.03 (s, 3 H, CH_3), 1.20 (t, 3 H, J = 7.0 Hz, CH_3). ^{13}C NMR: δ = 166.3, 164.0, 135.3, 132.9, 131.9, 129.9, 129.5, 128.2–127.4 (8 C), 110.4, 62.8, 46.7, 38.3, 32.2, 15.4, 13.7. ESI-MS (381.1): 382.4 (M + H^+). Found: C, 69.26; N, 3.67; S, 8.41; H, 6.08. $C_{22}H_{23}NO_3S$ requires C, 69.42; N, 3.55; S, 8.56; H, 6.24%.

4-Benzyl-5-methyl-2-phenyl-2,3-dihydro-4*H*-1,4-thiazin-3-one (16a). Column chromatography with 9 : 1 cyclohexane–AcOEt afforded **16a** (180 mg, 61%) as a yellow amorphous solid. IR (film) ν_{max}: 1654, 1310, 1177, 746, 693 cm^{-1}; ^1H NMR: δ = 7.42–7.18 (m, 10 H, Ar), 5.49 (s, 1 H, H-6), 5.23 and 4.88 (2 d, 2 H, J = 16.0 Hz, PhCH_2), 4.60 (s, 1 H, H-2), 1.90 (s, 3 H, CH_3). ^{13}C NMR: δ = 164.7, 137.1, 136.0, 135.1, 128.6–126.2 (10 C), 99.3, 46.3, 46.0, 20.1. ESI-MS (295.1): 334.4 (M + K^+). Found: C, 73.19; N, 4.74; S, 10.85; H, 5.80. $C_{18}H_{17}NOS$ requires C, 73.01; N, 4.55; S, 10.59; H, 5.53%.

4-Ethyl-5-methyl-2-phenyl-2,3-dihydro-4*H*-1,4-thiazin-3-one (17a). Column chromatography with 9 : 1 cyclohexane–AcOEt afforded **17a** (132 mg, 57%) as a white amorphous solid. IR (film) ν_{max}: 1654, 1310, 1245, 733, 696 cm^{-1}; ^1H NMR: δ = 7.35–7.25 (m, 5 H, Ar), 5.43 (s, 1 H, H-6), 4.46 (s, 1 H, H-2), 3.88 (dq, 1 H, $J_{1'a,Me}$ = 7.0 Hz, $J_{1'a,1'b}$ = 14.0 Hz), 3.74 (dq, 1 H, $J_{1'b,Me}$ = 7.0 Hz, $J_{1'a,1'b}$ = 14.0 Hz), 2.01 (s, 3 H, CH_3), 1.21 (t, 3 H, J = 7.0 Hz, CH_3). ^{13}C NMR: δ = 163.8, 135.6, 135.5, 128.3–127.7 (5 C), 98.4, 46.0, 38.2, 19.8, 13.9. ESI-MS (233.1): 234.3 (M + H^+). Found: C, 66.92; N, 6.00; S, 13.74; H, 6.48. $C_{13}H_{15}NOS$ requires C, 66.77; N, 6.26; S, 13.59; H, 6.31%.

4-Benzyl-2-(4-bromophenyl)-5-methyl-2,3-dihydro-4*H*-1,4-thiazin-3-one (16b). Column chromatography with 9 : 1 cyclohexane–AcOEt afforded **16b** (261 mg, 70%) as a white solid (MeOH). IR (film) ν_{max}: 1716, 1660, 1071, 1110, 730, 697 cm^{-1}; ^1H NMR: δ = 7.48–7.40 and 7.37–7.15 (2 m, 9 H, Ar), 5.49 (s, 1 H, H-6), 5.19 and 4.88 (2 d, 2 H, J = 16.0 Hz, PhCH_2), 4.53 (s, 1 H, H-2), 1.90 (s, 3 H, CH_3). ^{13}C NMR: δ = 164.3, 136.9, 136.1, 134.1, 131.5–126.2 (9 C), 121.9, 99.1, 46.0, 45.8, 20.1. ESI-MS (373.03): 412.9 (M + K^+). Found: C, 57.76; N, 3.74; S, 8.57; H, 4.31. $C_{18}H_{16}BrNOS$ requires C, 57.92; N, 3.57; S, 8.76; H, 4.50%.

2-(4-Bromophenyl)-4-ethyl-5-methyl-2,3-dihydro-4*H*-1,4-thiazin-3-one (17b). Column chromatography with 9 : 1 cyclohexane–AcOEt afforded **17b** (199 mg, 64%) as a yellow amorphous solid. IR (film) ν_{max}: 1658, 1611, 1303, 1108, 791, 733 cm^{-1}; ^1H NMR: δ = 7.45–7.18 (m, 4 H, Ar), 5.43 (s, 1 H, H-6), 4.40 (s, 1 H, H-2), 3.87 (dq, 1 H, $J_{1'a,Me}$ = 7.0 Hz, $J_{1'a,1'b}$ = 14.0 Hz), 3.74 (dq, 1 H, $J_{1'b,Me}$ = 7.0 Hz, $J_{1'a,1'b}$ = 14.0 Hz), 2.00 (s, 3 H, CH_3), 1.19 (t, 3 H, J = 7.0 Hz, CH_3). ^{13}C NMR: δ = 163.3, 135.7, 134.4, 131.4 (2 C), 129.5 (2 C), 121.8, 98.2, 45.6, 38.3, 19.8, 13.9. ESI-MS (311.0): 312.3 (M + H^+). Found: C, 50.01; N, 4.49; S, 10.27; H, 4.52. $C_{13}H_{14}BrNOS$ requires C, 50.29; N, 4.67; S, 10.05; H, 4.72%.

4-Benzyl-5-methyl-2-(*p*-tolyl)-2,3-dihydro-4*H*-1,4-thiazin-3-one (16c). Column chromatography with 9 : 1 cyclohexane–AcOEt afforded **16c** (15 mg, 5%) as a yellow amorphous solid. IR (film) ν_{max}: 1662, 1090, 1112, 734, 691 cm^{-1}; ^1H NMR: δ = 7.38–7.17 (m, 9 H, Ar), 5.43 (s, 1 H, H-6), 5.21 and 4.88 (2 d, 2 H, J = 16.0 Hz, PhCH_2), 4.53 (s, 1 H, H-2), 2.38 (s, 3 H, CH_3), 1.90 (s, 3 H, CH_3). ^{13}C NMR: δ = 165.1, 137.8, 137.3, 136.1, 132.2, 129.6–126.4 (9C), 99.5, 46.2, 46.1, 21.2, 20.3. ESI-MS (309.1): 332.3 (M + Na^+). Found: C, 73.75; N, 4.53; S, 10.35; H, 6.19. $C_{19}H_{19}NOS$ requires C, 73.93; N, 4.29; S, 10.51; H, 6.01%.

4-Ethyl-5-methyl-2-(*p*-tolyl)-2,3-dihydro-4*H*-1,4-thiazin-3-one (17c). Column chromatography with 9 : 1 cyclohexane–AcOEt afforded **17c** (24 mg, 10%) as a yellow amorphous solid. IR (film) ν_{max}:, 1653, 1375, 1311, 1125, 759 cm^{-1}; ^1H NMR: δ = 7.18 and 7.21 (2 d, 4 H, Ar), 5.41 (s, 1 H, H-6), 4.41 (s, 1 H, H-2), 3.87 (dq, 1 H, $J_{1'a,Me}$ = 7.0 Hz, $J_{1'a,1'b}$ = 14.0 Hz, H-1′a), 3.75 (dq, 1 H, $J_{1'b,Me}$ = 7.0 Hz, $J_{1'a,1'b}$ = 14.0 Hz, H-1′b), 2.27 (s, 3 H, CH_3), 2.01 (s, 3 H, CH_3), 1.21 (t, 3 H, J = 7.0 Hz, CH_3). ^{13}C NMR: δ = 164.2, 137.5, 135.5, 132.5, 129.1 (2 C), 127.6 (2 C), 98.4, 45.8, 38.3, 21.1, 19.9, 13.9. ESI-MS (247.1): 286.9 (M + K^+). Found: C, 67.98; N, 5.66; S, 12.96; H, 6.93. $C_{14}H_{17}NOS$ requires C, 67.79; N, 5.81; S, 12.77; H, 6.78%.

4-Ethyl-2-phenyl-2,3-dihydro-4*H*-benzo[*b*][1,4]thiazin-3-one (21). Column chromatography with 9 : 1 cyclohexane–AcOEt afforded **21** (53 mg, 20%) as a white amorphous solid. IR (film) ν_{max}: 1660, 1575, 1482, 1391, 1010, 745 cm^{-1}; ^1H NMR: δ = 7.38–7.19, 7.09–7.11, and 6.81–7.00 (3 m, 9 H, Ar), 4.65 (s, 1 H, H-2), 4.18 (dq, 1 H, $J_{1'a,Me}$ = 7.0 Hz, $J_{1'a,1'b}$ = 14.0 Hz), 4.04 (dq, 1 H, $J_{1'b,Me}$ = 7.0 Hz, $J_{1'a,1'b}$ = 14.0 Hz), 1.34 (t, 3 H, J = 7.0 Hz, CH_3). ^{13}C NMR: δ = 165.3, 139.0, 134.7, 128.7–127.2 (7 C), 123.4, 122.1, 116.9, 46.8, 40.8, 12.9. ESI-MS (269.1): 292.7 (M + Na^+). Found: C, 71.34; N, 5.20; S, 11.90; H, 5.61. $C_{16}H_{15}NOS$ requires C, 71.26; N, 5.45; S, 11.74; H, 5.48%.

2-(4-Bromophenyl)-4-ethyl-2,3-dihydro-4*H*-benzo[*b*][1,4]thiazin-3-one (22). Column chromatography with 9 : 1 cyclohexane-0AcOEt afforded **22** (62 mg, 18%) as a yellow amorphous solid. IR (film) ν_{max}: 1659, 1584, 1478, 1375, 1009, 747 cm^{-1}; ^1H NMR: δ = 7.40–6.95 (m, 8 H, Ar), 4.59 (s, 1 H, H-2), 4.16 (dq, 1 H, $J_{1'a,Me}$ = 7.0 Hz, $J_{1'a,1'b}$ = 14.0 Hz), 4.04 (dq, 1 H, $J_{1'b,Me}$ = 7.0 Hz, $J_{1'a,1'b}$ = 14.0 Hz), 1.35 (t, 3 H, J = 7.0 Hz, CH_3). ^{13}C NMR: δ = 164.9, 138.9, 133.8, 132.5–127.5 (6 C), 123.6, 122.0, 117.1, 46.4, 40.9, 13.0. ESI-MS (347.0): 348.9 (M + Na^+). Found: C, 55.18; N, 4.02; S, 9.21; H, 4.05. $C_{16}H_{14}BrNOS$ requires C, 55.01; N, 4.21; S, 9.04; H, 4.22%.

2,3-Dibenzyl-2,3-dihydro-2,2′-bibenzo[*d*]thiazole (23). Column chromatography of the crude 3CR (**18**/**2a**/H_2O; Method A) mixture with 15 : 1 cyclohexane–AcOEt afforded **23**[19] (180 mg, 40%) as a solid.

3,3′-Diethyl-3*H*,3′*H*-2,2′-spirobi[benzo[*d*]thiazole] (24). Column chromatography of the crude 3CR (**19**/**2a**/H_2O; Method A) mixture with 15 : 1 cyclohexane–AcOEt afforded **24** (125 mg, 40%) as a white amorphous solid. IR (film) ν_{max}: 1583, 1469, 1174, 1031, 727, 698 cm^{-1}; ^1H NMR: δ = 7.10–7.02 (m, 2 H, Ar), 6.78 (t, 1 H, Ar), 6.42 (d, 1 H, Ar), 3.45–3.20 (m, 2 H, CH_2CH_3), 1.21 (t, 3 H, J = 7.0 Hz, CH_3). ^{13}C NMR: δ = 141.1, 125.4, 122.9, 120.4, 118.6, 115.6, 106.5, 38.2, 12.6. ESI-MS (314.1): 337.5 (M + Na^+). Found: C, 64.93; N, 8.91; S, 20.39; H, 5.77. $C_{17}H_{18}N_2S_2$ requires C, 64.81; N, 8.77; S, 20.59; H, 5.55%.

Optimized one-pot two-step procedure (Method B) for the three-component synthesis of 1,4-thiazin-3-one derivatives 9, 15, 16, and 17

A solution of thiazolium salt (1.00 mmol) and α-diketone (1.00 mmol) in anhydrous DMF (2 mL) was vigorously stirred, degassed under vacuum, and saturated with argon (by an Ar-filled balloon) three times, then Et_3N (279 μL, 2.00 mmol) was added in one portion. The mixture was stirred at room temperature for 12 h, cooled to 0 °C and then diluted with ethanolic (75 vol%) 10% aqueous NaOH (0.80 mL, 2.00 mmol). The resulting mixture was stirred at 0 °C for 1 h and at room temperature for 2 h and then neutralized with 10% aqueous NH_4Cl and concentrated. The resulting residue was diluted with AcOEt (150 mL) and then washed with H_2O (2 × 20 mL). The organic

phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with the appropriate elution system to give the corresponding 1,4-thiazin-3-one derivative (Table 2). When 4,4′-dibromo benzil **2b** was used, the addition to the reaction mixture of a few drops of 1-methyl-2-pyrrolidinone (NMP) was required to obtain a fully homogeneous solution. The crude MCR mixtures containing compounds **9a** and **15a** were dissolved in pyridine (2 mL) and treated with benzoyl chloride (232 μL, 2.00 mmol) for 14 h to give the corresponding benzoylated derivatives **9a′** and **15a′**, which were purified by column chromatography.

9a: (244 mg, 72%); **9a′**: (389 mg, 88%); **15a**: (180 mg, 65%); **15a′**: (312 mg, 82%); **16a** (250 mg, 85%); **17a** (186 mg, 80%); **16b**: (335 mg, 90%); **17b**: (248 mg, 80%); **16c**: (105 mg, 34%); **17c**: **17c** (128 mg, 52%).

2-((Benzoyloxy)(phenyl)methyl)-3-benzyl-5-(2-hydroxyethyl)-4-methylthiazol-3-ium chloride (10a). A solution of thiazolium salt **3** (269 mg, 1.00 mmol) and α-diketone **2a** (210 mg, 1.00 mmol) in anhydrous DMF (2 mL) was vigorously stirred, degassed under vacuum, and saturated with argon (by an Ar-filled balloon) three times, then Et_3N (279 μL, 2.00 mmol) was added in one portion. The mixture was stirred at room temperature for 12 h and then concentrated to give **10a** (510 mg) at least 80% pure as established by ^{1}H NMR analysis. ^{1}H NMR (D_2O): δ = 7.60–7.00 (m, 13 H, Ar), 6.80–6.60 (m, 2 H, Ar), 5.70 and 5.59 (2d, 2 H, J = 16.0 Hz, PhCH_2), 5.52 (s, 1 H, H-1′), 3.76–3.68 (m, 2 H, H-2″), 3.05–2.60 (m, 2 H, H-1″), 2.24 (s, 3 H, CH_3). ^{13}C NMR: δ = 163.9, 144.4, 136.0, 134.1, 133.3, 132.5, 131.2, 130.6, 129.9–127.5 (13 C), 125.3, 70.9, 59.8, 54.6, 30.5, 12.9. ESI-MS (444.2): 444.2 (M^+).

^{18}O-Isotope labeling experiment. A solution of thiazolium salt **3** (54 mg, 0.20 mmol) and α-diketone **2a** (42 mg, 0.20 mmol) in anhydrous DMF (0.5 mL) was vigorously stirred, degassed under vacuum, and saturated with argon (by an Ar-filled balloon) three times, then Et_3N (55 μL, 0.40 mmol) was added in one portion. The mixture was stirred at room temperature for 12 h and then diluted with $H_2{}^{18}O$ (32 μL, 2.00 mmol). The resulting mixture was stirred for an additional 72 h, concentrated, and eluted from a column of silica gel with 3 : 1 cyclohexane–AcOEt to give ^{18}O-labelled **9a** (30 mg, 45%). HRMS (ESI/Q-TOF): calcd m/z for $C_{20}H_{22}NO^{18}OS$ $[M + H]^+$: 342.1408; found: 342.1420 (see Fig. S1†).

Optimized one-pot two-step procedure (Method C) for the four-component synthesis of 1,4-thian-3-one derivatives 9, 15, 16, 17, 21, and 22

A 0.5–2.0 mL process vial was filled with thiazole (1.30 mmol), alkyl bromide (1.00 mmol), and DMF (1 mL). The vial was sealed with a Teflon septum and aluminum crimp by using an appropriate crimping tool. The vial was then placed in its correct position in the Biotage Initiator cavity where irradiation for 20–30 min at 120 °C was performed. After the full irradiation sequence was completed, the vial was cooled to room temperature. The reaction mixture was diluted with a solution of α-diketone (1.00 mmol), Et_3N (279 μL, 2.00 mmol) in DMF (1 mL). The vial was irradiated again in the Biotage Initiator for 2 h at 100 °C, then cooled to room temperature, and concentrated. The resulting residue was diluted with AcOEt (150 mL) and then washed with H_2O (2 × 20 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with the appropriate elution system to give the corresponding 1,4-thiazin-3-one derivative (Table 2). When 4,4′-dibromo benzil **2b** was used, the addition to the reaction mixture of a few drops of 1-methyl-2-pyrrolidinone (NMP) was required to obtain a fully homogeneous solution. The crude MCR mixtures containing compounds **9a** and **15a** were dissolved in pyridine (2 mL) and treated with benzoyl chloride (232 μL, 2.00 mmol) for 14 h to give the corresponding benzoylated derivatives **9a′** and **15a′**, which were purified by column chromatography. Benzothiazin-3-one derivatives **21** and **22** were prepared under the previously described conditions starting from of benzothiazole (425 μL, 3.90 mmol), alkyl bromide (357 μL, 3.00 mmol), and DMF (1 mL).

9a: (122 mg, 36%); **9a′**: (234 mg, 53%); **15a**: (105 mg, 38%); **15a′**: (209 mg, 55%); **16a**: (165 mg, 56%); **17a**: (119 mg, 51%); **16b**: (227 mg, 61%); **17b**: (180 mg, 58%); **16c**: (24 mg, 8%); **17c**: (37 mg, 15%); **21**: (113 mg, 42%); **22**: (156 mg, 45%).

Crystal data for compound 16b

X-Ray diffraction data for compound **16b** were collected on a Nonius Kappa CCD diffractometer, at room temperature (T = 295 K), with graphite monochromated Mo Kα radiation (λ = 0.7107 Å). The data sets were integrated with the Denzo-SMN package[24] and corrected for Lorentz, polarization and absorption effects (SORTAV).[25] The structure was solved by direct methods (SIR97)[26] and refined (SHELXL-97)[27] by full matrix least squares with anisotropic non-H and isotropic H atoms. ORTEP[28] view of the molecule is shown in Fig. 1. $C_{18}H_{16}BrNOS$; monoclinic, space group $P2_1/c$, a = 12.0158(5), b = 9.3261(4), c = 14.7056(6) Å, β = 98.300(3)°, V = 1630.7(1) Å^3, Z = 4, D_c = 1.525 g cm^{-3} . Intensity data collected with $\theta \leq 26.0°$; 3147 independent reflections measured; 2242 reflections observed [$I > 2\sigma(I)$]. Final R = 0.0438 (observed reflections) and Rw = 0.1098 (all reflections), N. Parameters = 263, GOF = 1.051. CCDC 875932.†

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