# 2-Substituted 5-Acetyl-4-Thiazolyl Triflates as Useful Building Blocks for the Preparation of Functionalized Thiazoles

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**Keywords:** Heterocycles / Thiazoles / Pyrido[3,4-*c*]thiazoles / Triflates / Palladium

The readily available 2-substituted 5-acetyl-4-thiazolyl triflates **2** are useful building blocks for the preparation of functionalised thiazoles by means of palladium-catalysed cross-coupling reactions with organometallic reagents and alkoxycarbonylation and deoxygenation reactions. The combination of palladium-catalysed coupling of **2** together with 1-alkynes/6-*endo-dig* annulation reactions in the presence of ammonia leads to functionalised pyrido[3,4-*c*]thiazoles in satisfactory yields. The utilisation of uncatalysed displacement reactions of the triflate group represents a very simple method for the synthesis of 4-*N*-,4-*O*-, and 4-*S*-substituted thiazoles.

## Introduction

The presence of the thiazole moiety in the structures of several naturally occurring molecules with important antibiotic, endothelin-converting enzyme inhibitor, antitumor, and immunosuppressive properties has been known for several years.[1] In the last two decades, a new group of metabolites derived from amino acids and containing a thiazole ring have been isolated from marine species and have been shown to exhibit antineoplastic and cytotoxic activity. The possibility of these systems acting as metal-ion-chelating compounds has also been suggested.[2] Diarylthiazoles are commonly reported as selective cyclooxygenase-2 (COX-2) inhibitors.[3] The aminothiazole ring system has found applications in drug development for the treatment of allergies, hypertension, inflammation, schizophrenia, bacterial and HIV infections.[4] A series of 2-(alkylguanidino)-4-furylthiazoles and related compounds were synthesized and evaluated for antimicrobial activity against *Helicobacter pylori*, inhibitory effect on gastric acid secretion, and histamine $H_2$-receptor antagonist activity.[5] In vitro cytotoxicity of a large number of condensed thiazoles has been tested against several cell lines and some tricyclic fused derivatives were synthesised as potential $\alpha_1$-adrenoceptor antagonists.[6] These properties have spurred considerable structural and synthetic efforts.[7] Given this proven utility, it seems reasonable that the development of new synthetic methods for functionalised thiazoles and fused thiazoles might provide additional lead molecules for use in drug discovery.

In connection with our ongoing interest in developing new synthetic strategies for the construction of heterocyclic rings, we have recently focused our attention on the synthesis of 2-substituted 5-acetyl-4-hydroxythiazoles **1** by reaction of conjugated azoalkenes with aryl thioamides[8] and subsequent removal of the NH-BOC-hydrazo protecting group.[9] We thought that their 2-substituted 5-acetyl-4-thiazolyl triflate derivatives **2** (Scheme 1) could represent the starting building block for the preparation of functionalised thiazoles. Due to the excellent leaving-group properties of the trifluoromethanesulfonate the scope of the application of triflates in organic synthesis has broadened enormously.[10] Although some reports of palladium-catalysed coupling reactions of halothiazoles, bromine and iodine-containing isothiazoles and 2-halo-$\Delta^2$-thiazolines have appeared in the literature,[11] no examples of palladium-catalysed coupling exist for thiazolyl triflates. We assumed that the choice of the trifluoromethanesulfonate as a leaving group is a key point to obtain fruitful results for the introduction of a functionalised carbon side chain into these heteroaromatics.[12] We have reported preliminary investigations[13] that demonstrate that the combined palladium-catalysed coupling of 2-substituted 5-acetyl-4-thiazolyl triflates with alkynes/annulation reactions could represent an expeditious procedure for the synthesis of pyrido[3,4-*c*]thiazoles. With the purpose of developing the heterocyclic ring structures of the title using thiazolyl triflates as starting building blocks, we now wish to report the full details of the results we have obtained, as well as the scope and limitations of this synthetic methodology. Our goal during this work was to provide a clean, high-yielding, general synthesis of functionalised thiazoles.

## Results and Discussion

Treatment of readily available 2-substituted 5-acetyl-4-hydroxythiazoles **1a−g** with $Tf_2O$ and 2,6-di-*tert*-butyl-4-methylpyridine ($CH_2Cl_2$, room temp.) provided chemoselec-

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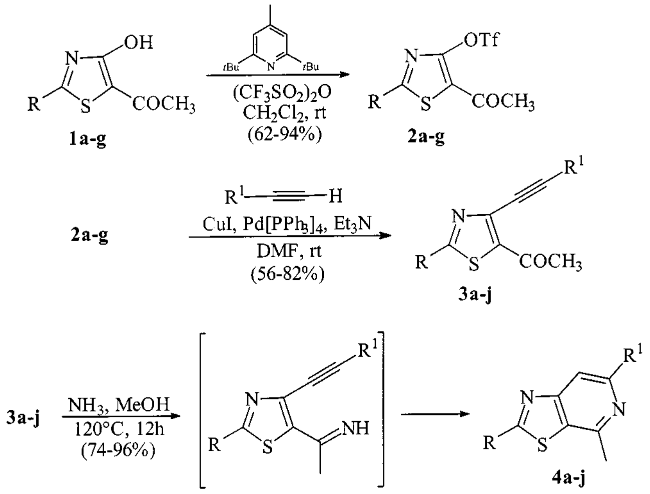
tively triflates **2a−g** in good to high yields (65−94%).[14] The triflates **2a−g** undergo palladium-catalysed coupling with 1-alkynes,[15] at room temperature, to afford the 2-substituted 5-acetyl-4-alkynylthiazoles **3a−j** (45−95% yield). The subsequent treatment of **3** with ammonia in MeOH leads to the formation of the pyrido[3,4-*c*]thiazoles **4a−j** in excellent yields (74−96%) (Scheme 1 and Table 1) through sequential addition/elimination/cycloamination reactions.



Scheme 1. Palladium-catalysed alkynylation of 2-substituted 5-acetyl-4-thiazolyl triflates **2** and sequential addition/elimination/cycloamination reactions of 2-substituted 5-acetyl-4-alkynylthiazoles **3** to pyrido[3,4-*c*]thiazoles **4**

The reaction mechanism probably involves the formation of an imine that undergoes a regioselective 6-*endo-dig* cyclization to give **4**.[16] The regioselective outcome of the annulation reaction (6-*endo-dig* cyclization vs. 5-*exo-dig* cyclization) can be determined by the suitable choice of the starting γ-ketoalkyne derivative: the sequential addition/elimination/cycloamination of 4-pentinones gave 2,3,5-substituted pyrroles and fused pyrrole systems,[17] while the presence of a γ-ketoalkyne moiety in an aromatic framework is responsible for the 6-*endo-dig* cyclization.

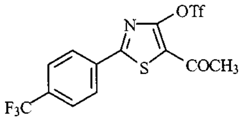
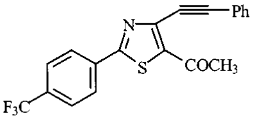
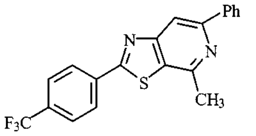
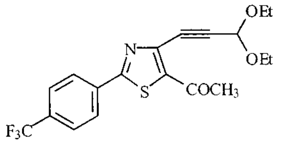
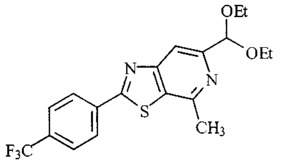
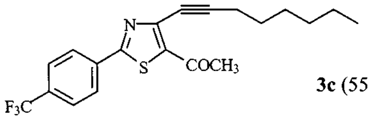
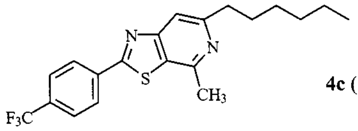
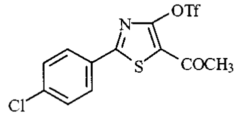
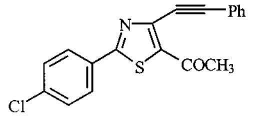
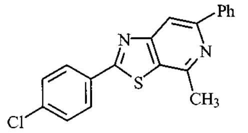
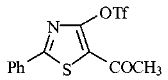
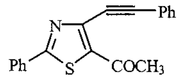
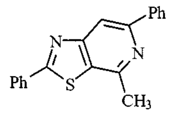
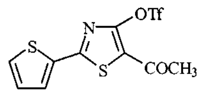
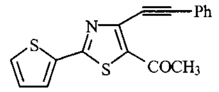
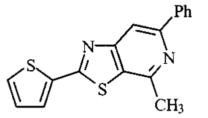
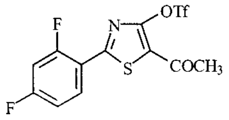
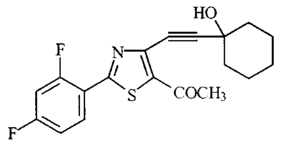
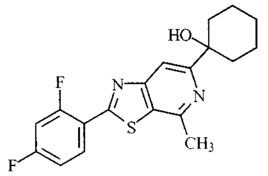
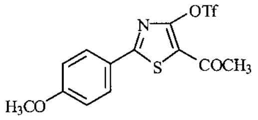
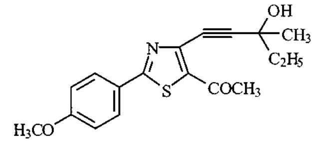
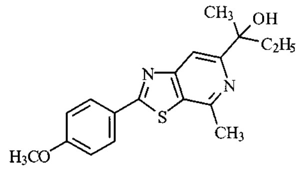
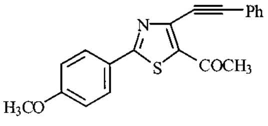
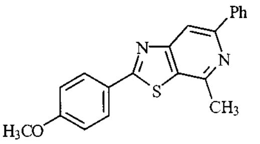
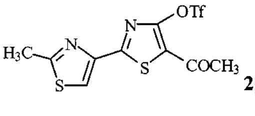
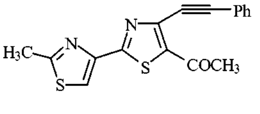
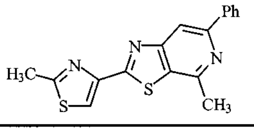
In the last few years a strong impact for the application of triflates in organic synthesis came from the discovery of their cross-coupling reactions with different organometallic compounds which proceed under mild conditions and tolerate the presence of various functional groups.[18] Thus, the reaction of **2c** with tributyl(vinyl)stannane and **2b** with 2-(tribultylstannyl)thiophene in the presence of 2 mol-% Pd[$(PPh_3)$]$_4$ and 3 equiv. LiCl in 1,4-dioxane at 90°C,[19] gave the coupling products **5a**, **b** in 90 and 95% yield respectively. Analogously, the palladium-catalysed cross-coupling reactions of **2c**, **g** with arylboronic acids accomplished the preparation of **5c**, **d** in excellent yields (Scheme 2, Table 2).[20]

It was also to be expected that the thiazolylpalladium(II) species produced from the oxidative addition of aryl triflates to a palladium(0) complex might undergo alkoxycarbonylation reactions with carbon monoxide and alcohols to afford the corresponding esters.[21] The representative results (Scheme 3, Table 2) shows that the carbonylation reaction can be successfully applied to the aromatic thiazolyl ring under the presence of a 1,1′-bis(diphenylphosphanyl)-ferrocene(DPPF)/Pd(OAc)$_2$ catalytic system in DMF or toluene. The use of DPPF instead of triphenylphosphane proved to be essential for the reactions to proceed significantly. In fact, in a typical procedure a mixture of **2c** (0.9 mmol), triethylamine (1.8 mmol), palladium acetate (0.027 mmol), triphenylphosphane (0.054 mmol), and MeOH (18 mmol) in DMF purged with carbon monoxide and stirred under a CO balloon at room temp. for 5 h gave the corresponding carboxymethyl derivative **5e** in 15% yield. The main reaction product (50%) was the 5-acetyl-4-hydroxy-2-phenylthiazole (**1c**) derived from the triflate hydrolysis. The replacement of triphenylphosphane by 1 mol of DPPF per mol of palladium dramatically improved the reaction yield (55%). The best result was obtained in toluene at 60°C (65%) because the competitive hydrolysis of triflate did not occur.

We carried out the selective deoxygenation of the thiazolyl triflate derivatives utilizing tributylammoniun formate as the hydrogen donor in the presence of a homogeneous palladium catalyst.[22] The hydrogenolysis of aryl triflates with molecular hydrogen over a heterogenous transition-metal catalyst (e.g. Pd/C) has been described.[23] The replacement of molecular hydrogen by tri-*n*-butylammonium formate as the hydrogen donor in a homogeneous-catalysed hydrogen-transfer reaction provided therefore an efficient and chemoselective route for the reductive cleavage of carbon−oxygen bonds of thiazolyl triflates **2** to give in high yields the 2-substituted 5-acetylthiazoles **6** (Scheme 3). Typical results are given in the Table 2. As in the case of carbonylation reactions, reductions of triflates **2**, too, are dependent upon phosphane ligand and solvent. The recourse to DPPF and toluene is beneficial to reduction reactions that do not proceed under the presence of triphenylphosphane in DMF because the competitive hydrolysis of the triflate is faster than the deoxygenation [e.g., the 4-hydroxythiazolyl derivative **1c** was recovered in 95% yield when **2c** treated with 2 mol-% of Pd(OAc)$_2$(PPh$_3$)$_2$, 2 equiv. of HCOOH, 3 equiv. of $n$Bu$_3$N in DMF at 60 °C for 1 h].

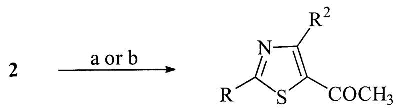
Based on the previously reported results on the palladium-catalysed reaction of 4-halothiazoles with phenylsulfonylacetonitrile under basic conditions[24] and nucleophilic substitution of 2-halothiazole, even without addition of a palladium complex,[25] we have developed a new and simple method for the synthesis of 4-*N*-, 4-*O*-, and 4-*S*-substituted thiazoles. The utilization of displacement reactions of the triflate group for the preparation of amines, ethers, and sulfides has been applied in the palladium- and nickel-catalysed carbon−heteroatom bond formation through reductive elimination of palladium or nickel(II)amido/oxo/thiolato complexes derived from the oxidative addition of the Pd$^0$ or Ni$^0$ on aryl triflates;[26] in the uncatalysed amination of aryl triflates in refluxing acetonitrile or under pressure (with triflates bearing electron-withdrawing substituents);[27] in the uncatalysed amination of aryl triflates

Table 1. Synthesis of 2-substituted 5-acetyl-4-thiazolyl triflates **2**, 2-substituted 5-acetyl-4-alkynylthiazoles[a] **3**, and pyrido[3,4-*c*]thiazoles **4**[b]

| Recovered **2** (% Yield) | Recovered **3** (% Yield) | Recovered **4** (% Yield) |
|---|---|---|
|  **2a** (86) |  **3a** (62) |  **4a** (82) |
|  |  **3b** (76) |  **4b** (92) |
|  |  **3c** (55) |  **4c** (90) |
|  **2b** (77) |  **3d** (78) |  **4d** (96) |
|  **2c** (94) |  **3e** (82) |  **4e** (74) |
|  **2d** (65) |  **3f** (87) |  **4f** (88) |
|  **2e** (93) |  **3g** (84) |  **4g** (75) |
|  **2f** (75) |  **3h** (62) |  **4h**(90) |
|  |  **3i** (95) |  **4i** (81) |
|  **2g** (70) |  **3j** (76) |  **4j** (92) |

[a] Unless otherwise stated, the synthesis of 2-substituted 5-acetyl-4-alkynylthiazoles **3** was carried out in DMF at room temp., using the following molar ratios: **2**/alkyne/$Et_3N$/CuI/$Pd(PPh_3)_4$ = 1:1.2:20:0.02:0.04. – [b] Unless otherwise stated, the synthesis of pyrido[3,4-*c*]thiazoles **4** was carried out in ammonia, 2.0 M solution in methyl alcohol at 120°C; yields refer to single runs and are given for isolated products

proceeding through the intermediacy of arynes;[28] in the preparation of benzodiazepines;[29] in the preparation of $N^2$-alkylated deoxyguanosines and amination of nitrogen-containing heterocycles.[30] The latter reaction, which produces amino derivatives of nitrogen-containing heterocycles deals, however, with the chemistry of peculiar substrates,



**5a-d**

Scheme 2. Palladium-catalysed reactions of 2-substituted 5-acetyl-4-thiazolyl triflates **2** with organostannanes and boronic acids: a = $n\mathrm{Bu_3SnR^2}$, $\mathrm{Pd(PPh_3)_4}$, LiCl, dioxane, 90°C; b = $\mathrm{R_2B(OH)_3}$, $\mathrm{K_2CO_3}$, $\mathrm{Pd(PPh_3)_4}$, toluene, 90°C

giving rise to the question of whether the presence of the thiazolyl ring allows the substitution of the amino/oxo/thiolate groups for the triflate to occur under uncatalysed mild conditions. Therefore, because of the intense interest in biologically active heterosubstituted thiazoles, we explored the scope of this reaction. The thiazolyl triflates **2a**, **c** reacted with an excess of secondary amines to afford the corresponding amino derivative **5g**, **h**. Analogously the reaction of **2g** with an excess of 4-methoxy-α-toluenethiol in the presence of 1,8-diazabicyclo[5.4.0]undece-7-ene (DBU) as base in toluene gave the sulfide **5i**; alcoholysis with ethanol under reflux in the presence of DBU of **2c** led to the 4-ethoxythiazolyl derivative **5j** (Scheme 4, Table 2).

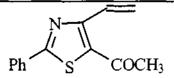
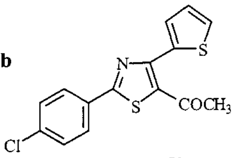
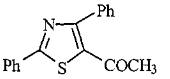
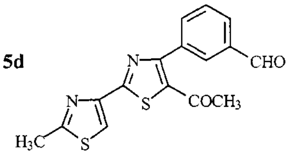
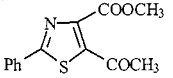
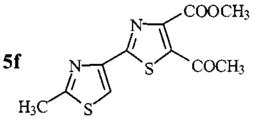
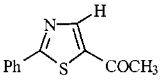
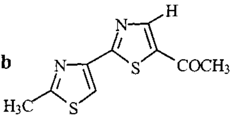
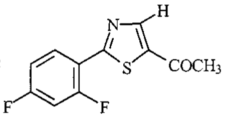
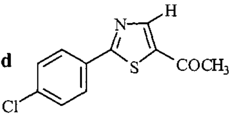
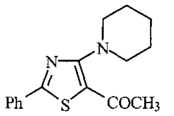
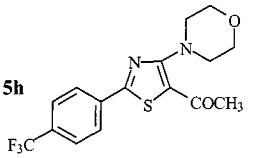
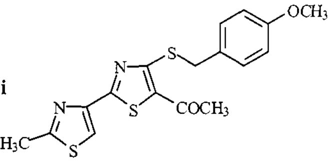
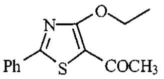
The reaction of **2c** with phenylhydrazine refluxed in ethanol gave a mixture of **5j** (47%) and the 5-hydrazono-2-phenyl-4-thiazolyl triflate (**7**) (39%). The hydrazone **7** was also isolated in 56% yield when the reaction was carried out in DMSO at 60°C. Interestingly the pyrazolo[3,4-*d*]thiazole (**8**) resulted from heating **2c** with phenylhydrazine in refluxing toluene. This result demonstrates that with the hydrazinic group the nucleophilic addition to the carbonyl group is faster than the nucleophilic displacement of the triflate.

Further work is in progress in order to evaluate the scope and the limitation of the reactions of the triflates **2** with bidentate nucleophiles, and in particular our efforts are towards the optimization of the reaction conditions.

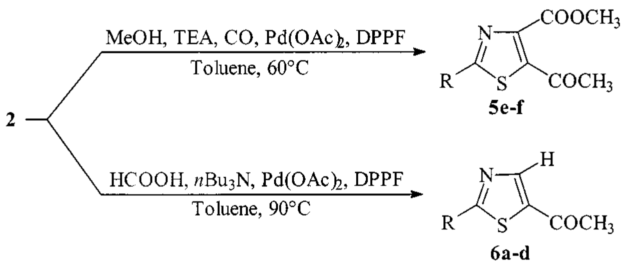
## Conclusion

To sum up, we have shown that the ready available 2-substituted 5-acetyl-4-thiazolyl triflates **2** are useful building blocks for the preparation of fuctionalised thiazoles by means of palladium-catalysed cross-coupling reactions with organometallic reagents, alkoxycarbonylation reactions and deoxygenation reactions. The combined palladium-catalysed coupling of **2** with 1-alkynes/6-*endo-dig* annulation reactions in the presence of ammonia led in satisfactory yields to functionalised pyrido[3,4-*c*] thiazoles. The utilization of uncatalysed displacement reactions of the triflate group represents a very simple method for the synthesis of 4-*N*-, 4-*O*-, and 4-*S*-substituted thiazoles. The sequential nucleophilic addition/nucleophilic displacement reactions of **2** with bidentate nucleophiles may result in an easy access to fused thiazoles

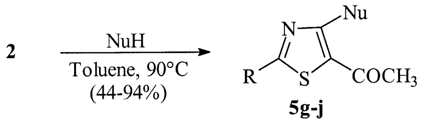
Table 2. Synthesis of 2,4-disubstituted 5-acetylthiazoles **5** and 2-substituted 5-acetylthiazoles **6**[a]

| Compound | Yield (%) | t °C | Solvent |
|---|---|---|---|
| **5a**  | 90 | 90 | dioxane |
| **5b**  | 95 | 90 | dioxane |
| **5c**  | 75 | 90 | toluene |
| **5d**  | 93 | 90 | toluene |
| **5e**  | 65 | 60 | toluene |
| **5f**  | 64 | 60 | toluene |
| **6a**  | 80 | 90 | toluene |
| **6b**  | 96 | 90 | toluene |
| **6c**  | 94 | 90 | toluene |
| **6d**  | 85 | 90 | toluene |
| **5g**  | 64 | 90 | toluene |
| **5h**  | 94 | 90 | toluene |
| **5i**  | 69 | 90 | toluene |
| **5j**  | 44 | 78 | ethanol |

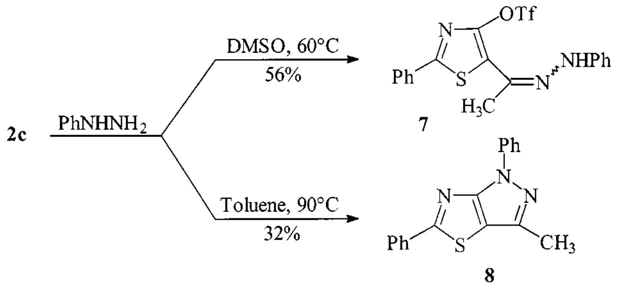
[a] Yields refer to single runs and are given for isolated products



Scheme 3. Palladium-catalysed alkoxycarbonylation and reduction reactions of 2-substituted 5acetyl-4-thiazolyl triflates **2**



Scheme 4. Displacement reactions of 2-substituted 5acetyl-4-thiazolyl triflates **2** with nucleophiles: NuH = piperidine, morpholine, 4-methoxyphenylmethanethiol, ethanol



Scheme 5. Reactions of 5-acetyl-2-phenyl-4-thiazolyl triflates **2c** with phenylhydrazine

## Experimental Section

**General:** Melting points were not corrected and were measured with a Büchi apparatus. – $^1$H-NMR (200 MHz) and $^{13}$C-NMR (50.3 MHz) spectra ($CDCl_3$, unless otherwise stated; TMS as internal standard) were recorded with a Bruker AC 200 E spectrometer. – EI (70 eV) mass spectra were recorded with a TSQ 700 Finnigan/Mat or Shimadzu QP-5000 instrument. – IR spectra were recorded in KBr dispersions unless otherwise indicated. – The 2-substituted 5-acetyl-4-hydroxythiazoles **1a–g** were prepared according to the previously described method.[9] The 2-substituted 5-acetyl-4-thyazolyl triflates **2** were prepared according to ref.[14] and were purified by chromatography on silica gel eluting with *n*-hexane/EtOAc mixtures. All starting materials, catalysts, ligands, bases, and solvents if not already stated, are commercially available and were used as purchased, without further purification. Reaction products were purified by flash chromatography on silica gel eluting with *n*-hexane/EtOAc mixtures. All isolated new products gave satisfactory microanalyses.

**2a:** Purified by flash chromatography (*n*-hexane/EtOAc, 85:15). – White solid. – M.p. 91–92°C. – Yield 86%. – IR (KBr): $\tilde{\nu}$ = 1675 cm$^{-1}$, 1610, 1510, 1440, 1220, 1135, 770, 735, 700. – $^1$H NMR ($CDCl_3$): δ = 2.68 (s, 3 H), 7.73 and 8.04 (AA′–BB′ system, 4 H, *J* = 8.7 Hz). – $^{13}$C NMR ($CDCl_3$): δ = 29.19, 115.50, 121.88, 126.17, 126.41, 133.08 (q), 149.51, 167.80, 187.88. – EI MS; *m*/*z* (relative intensity): 419 (51) [M$^+$], 340 (10), 87 (61), 69 (100). – $C_{13}H_7F_6NO_4S_2$ (419.31): calcd. C 37.24, H 1.68, F 27.19, N 3.34, O 15.26, S 15.29; found C 37.29, H 1.71, N 3.30.

**2b:** Purified by flash chromatography (*n*-hexane/EtOAc, 70:30). – White solid. – M.p. 129–130°C. – Yield 77%. – IR (KBr): $\tilde{\nu}$ = 1670 cm$^{-1}$, 1600, 1530, 1440, 1230, 1120, 790, 740, 720. – $^1$H NMR ($CDCl_3$): δ = 2.64 (s, 3 H), 7.37 and 7.87 (AA′-BB′ system, 4 H, *J* = 8.2 Hz). – $^{13}$C NMR ($CDCl_3$): δ = 29.11, 121.75, 125.11, 127.70, 129.98, 136.82, 149.30, 166.45, 187.79. – EI MS; *m*/*z* (relative intensity): 385 (74) [M$^+$], 306 (18), 224 (24), 180 (77), 87 (93), 69 (100). – $C_{12}H_7F_3ClNO_4S_2$ (385.76): calcd. C 37.36, H 1.83, F 14.77, Cl 9.19, N 3.63, O 16.59, S 16.62; found C 37.29, H 1.75, N 3.72.

**2c:** Purified by flash chromatography (*n*-hexane/EtOAc, 85:15). – White solid. – M.p. 64–65°C. – Yield 94%. – IR (KBr): $\tilde{\nu}$ = 1685 cm$^{-1}$, 1530, 1440, 1235, 1140, 740. – $^1$H NMR ($CDCl_3$): δ = 2.61 (s, 3 H), 7.38–7.51 (m, 3 H), 7.86–7.91 (m, 2 H). – $^{13}$C NMR ($CDCl_3$): δ = 29.16, 115.50, 121.89, 126.51, 129.36, 132.59, 149.39, 169.85, 187.87. – EI MS; *m*/*z* (relative intensity): 351 (22) [M$^+$], 272 (10), 190 (24), 146 (100), 104 (60), 87 (45), 69 (66). – $C_{12}H_8F_3NO_4S_2$ (351.32): calcd. C 41.03, H 2.30, F 16.22, N 3.99, O 18.22, S 18.25; found C 40.95, H 2.24, N 3.85.

**2d:** Purified by flash chromatography (*n*-hexane/EtOAc, 75:25). – Yellow solid. – M.p. 97–98°C. –Yield 65%. – IR (KBr): $\tilde{\nu}$ = 1660 cm$^{-1}$, 1510, 1410, 1220, 1115. – $^1$H NMR ($CDCl_3$): δ = 2.63 (s, 3 H), 7.11–7.15 (m, 1 H), 7.56–7.59 (m, 1 H), 7.65–7.87 (m, 1 H). – $^{13}$C NMR ($CDCl_3$): δ = 29.05, 115.42, 121.61, 126.73, 129.41, 131.77, 149.43, 163.62, 187.76. – EI MS; *m*/*z* (relative intensity): 357 (59) [M$^+$], 196 (23), 152 (100), 110 (37), 87 (36), 69 (70). – $C_{10}H_6F_3NO_4S_3$ (357.34): calcd. C 33.61, H 1.69, F 15.95, N 3.92, O 17.91, S 26.92; found C 33.70, H 1.70, N 4.07.

**2e:** Purified by flash chromatography (*n*-hexane/EtOAc, 85:15). – White solid. – M.p. 86–87°C. – Yield 93%. – IR (KBr): $\tilde{\nu}$ = 1660 cm$^{-1}$, 1610, 1515, 1425, 1220, 1110, 790, 740. – $^1$H NMR ($CDCl_3$): δ = 2.65 (s, 3 H), 7.05–7.27 (m, 2 H), 8.16–8.30 (m, 1 H). – $^{13}$C NMR ($CDCl_3$): δ = 29.28, 104.43, 104.94, 113.30 (d), 116.61, 130.62 (d), 158.87, 162.57, 164.40, 167.69, 186.09. – EI MS; *m*/*z* (relative intensity): 387 (46) [M$^+$], 308 (17), 182 (37), 139 (14), 87 (38), 69 (100). – $C_{12}H_6F_5NO_4S_2$ (387.30): calcd. C 37.21, H 1.56, F 24.53, N 3.62, O 16.52, S 16.56; found C 37.31, H 1.58, N 3.74.

**2f:** Purified by flash chromatography (*n*-hexane/EtOAc, 80:20). – Yellow solid. – M.p. 110–111°C. – Yield 75%. – IR (KBr): $\tilde{\nu}$ = 1670 cm$^{-1}$, 1600, 1520, 1435, 1230, 1120, 800, 725. – $^1$H NMR ($CDCl_3$): δ = 2.61 (s, 3 H), 3.86 (s, 3 H), 6.94 and 7.74 (AA′-BB′ system, 4 H, *J* = 9.7 Hz). – $^{13}$C NMR ($CDCl_3$): δ = 29.05, 55.56, 114.64, 121.83, 123.50, 128.30, 149.36, 163.22, 169.79, 187.85. – EI MS; *m*/*z* (relative intensity): 381 (23) [M$^+$], 176 (37), 134 (100), 69 (48). – $C_{13}H_{10}F_3NO_5S_2$ (381.34): calcd. C 40.95, H 2.64, F 14.95, N 3.67, O 20.98, S 16.81; found C 40.99, H 2.66, N 3.80.

**2g:** Purified by flash chromatography (*n*-hexane/EtOAc, 75:25). – Yellow solid. – M.p. 84–85°C. – Yield 70%. – IR (KBr): $\tilde{\nu}$ = 1660 cm$^{-1}$, 1510, 1410, 1230, 1115. – $^1$H NMR ($CDCl_3$): δ = 2.62 (s, 3 H), 2.76 (s, 3 H), 7.94 (s, 1 H). – $^{13}$C NMR ($CDCl_3$): δ = 19.18, 29.33, 115.46, 120.18, 124.61, 126.17, 147.12, 167.95, 187.91. – EI MS; *m*/*z* (relative intensity): 372 (35) [M$^+$], 219 (14), 167 (20), 125 (100), 83 (19), 69 (46). – $C_{10}H_7F_3N_2O_4S_3$ (372.35): calcd. C 32.26, H 1.89, F 15.31, N 7.52, O 17.19, S 25.83; found C 32.16, H 1.87, N 7.49.

**2-Substituted 5-Acetyl-4-alkynylthiazoles 3a–j. – General Procedures:** This is exemplified by the reaction of 5-acetyl-2-phenyl-4-thiazolyl triflate (**2c**) with phenylacetylene. To a solution of 5-acetyl-2-phenyl-4-thiazolyl triflate (**2c**) (0.340 g, 0.97 mmol) in DMF (4 mL), phenylacetylene (0.118 g, 1.16 mmol), triethylamine

(2.7 mL), CuI (0.004 g, 0.019 mmol), and tetrakis(triphenylphosphane)palladium(0) were added. The reaction mixture was gently purged with nitrogen and stirred at room temperature for 12 h under a nitrogen atmosphere. Then, diethyl ether and 0.1 N HCl were added; the organic layer was separated, washed with water, dried ($Na_2SO_4$), and concentrated at reduced pressure. The residue was purified by flash chromatography eluting with a 90:10 *n*-hexane/EtOAc mixture to give **3e** (0.241 g, 82% yield).

**3a:** Purified by flash chromatography (*n*-hexane/EtOAc, 95:5). − White solid. − M.p. 153−154°C. − Yield 62%. − IR (KBr): $\tilde{\nu}$ = 2180 $cm^{-1}$, 1660, 1500, 740. − $^1H$ NMR ($CDCl_3$): δ = 2.85 (s, 3 H), 7.39−7.45 (m, 5 H), 7.65 and 8.09 (AA′-BB′ system, 4 H, *J* = 8.2 Hz). − $^{13}C$ NMR ($CDCl_3$): δ = 29.10, 83.75, 97.16, 121.35, 126.11, 126.18, 127.36, 128.69, 129.92, 131.67,132.00(q), 135.03, 169.67, 190.58. − EI MS; *m*/*z* (relative intensity): 371 (44) [$M^+$], 356 (15), 189 (23), 157 (100), 113 (74). − $C_{20}H_{12}F_3NOS$ (371.38): calcd. C 64.68, H 3.26, F 15.35, N 3.77, O 4.31, S 8.63; found C 64.12, H 3.23, N 3.70.

**3b:** Purified by flash chromatography (*n*-hexane/EtOAc, 80:20). − White solid. − M.p. 97−98°C; yield 76%. − IR (KBr): $\tilde{\nu}$ = 1660 $cm^{-1}$, 1310, 760, 680. − $^1H$ NMR ($CDCl_3$): δ = 1.27 (t, 6 H), 2.80 (s, 3 H), 3.69 (q, 4 H), 5.58 (s, 1 H), 7.72 and 8.10 (AA′-BB′ system, 4 H, *J* = 8.4 Hz). − $^{13}C$ NMR ($CDCl_3$): δ = 15.10, 29.11, 61.56, 78.95, 91.73, 92.49, 126.16, 126.24, 127.39, 133.47(q), 136.32, 143.53, 169.65, 190.45. − EI MS; *m*/*z* (relative intensity): 397 (5) [$M^+$], 368 (32), 353 (60), 352 (73), 324 (100), 296 (77). − $C_{19}H_{18}F_3NO_3S$ (397.44): calcd. C 57.42, H 4.57, F 14.34, N 3.52, O 12.08, S 8.07; found C 57.78, H 4.53, N 3.58.

**3c:** Purified by flash chromatography (*n*-hexane/EtOAc, 90:10). − Oil. − Yield 55%. − IR (neat): $\tilde{\nu}$ = 2120 $cm^{-1}$, 1660, 1320. − $^1H$ NMR ($CDCl_3$): δ = 0.82(t, 3 H), 1.25−1.31 (m, 8 H), 1.66 (t, 2 H), 2.60 (s, 3 H), 7.72 and 8.11 (AA′-BB′ system, 4 H, *J* = 8.0 Hz). − $^{13}C$ NMR ($CDCl_3$): δ = 14.05,19.23, 19.64, 22,54, 26.08, 76.41, 100.15, 126.09, 127.35, 127.39, 190.83. − EI MS; *m*/*z* (relative intensity): 379 (17) [$M^+$], 336 (30), 322 (66), 309 (100). − $C_{20}H_{20}F_3NOS$ (379.44): calcd. C 63.31, H 5.31, F 15.02, N 3.69, O 4.22, S 8.45; found C 63.12, H 5.15, N 3.51.

**3d:** Purified by flash chromatography (*n*-hexane/EtOAc, 90:10). − White solid. − M.p. 156−157°C. − Yield 78%. − IR (KBr): $\tilde{\nu}$ = 2175 $cm^{-1}$, 1650, 800, 730. − $^1H$ NMR ($CDCl_3$): δ = 2.87 (s, 3 H), 7.26−7.44 (m, 5 H), 7.62 and 7.93 (AA′-BB′ system, 4 H, *J* = 6.7 Hz); $^{13}C$ NMR ($CDCl_3$): δ = 29.01, 83.82, 96.68, 121.34, 126.20, 126.57, 129.31, 130.64, 131.76, 137.74, 170.23, 190.48. − EI MS; *m*/*z* (relative intensity): 339 (36) [$M^+$ + 2], 338 (22) [$M^+$ + 1], 337 (90) [$M^+$], 322 (41), 157 (100). − $C_{19}H_{12}ClNOS$ (337.82): calcd. C 67.55, H 3.58, Cl 10.49, N 4.15, O 4.74, S 9.49; found C 67.33, H 3.68, N 4.28.

**3e:** Purified by flash chromatography (*n*-hexane/EtOAc, 95:5).[13]

**3f:** Purified by flash chromatography (*n*-hexane/EtOAc, 85:15). − Yellow solid. − M.p. 150−152°C. − Yield 87%. − IR (KBr): $\tilde{\nu}$ = 2170 $cm^{-1}$, 1650. − $^1H$ NMR ($CDCl_3$): δ = 2.84 (s, 3 H), 7.08−7.64 (m, 8 H). − $^{13}C$ NMR ($CDCl_3$): δ = 29.02, 84.46, 97.01, 121.45, 128.37, 128.61, 129.11, 129.77, 130.45, 131.83, 135.99, 165.39, 190.48. − EI MS; *m*/*z* (relative intensity): 309 (94) [$M^+$], 294 (56), 157 (100), 127 (39), 113 (53). − $C_{17}H_{11}NOS_2$ (309.40): calcd. C 66.99, H 3.58, N 4.53, O 5.17, S 20.72; found C 66.58, H 3.54, N 4.68.

**3g:** Purified by flash chromatography (*n*-hexane/EtOAc, 70:30). − White solid. − M.p. 154−156°C. − Yield 84%. − IR (KBr): $\tilde{\nu}$ = 3230 $cm^{-1}$, 1650, 1600, 1525, 740, 720. − $^1H$ NMR ($CDCl_3$): δ = 1.25−1.78 (m, 10 H), 2.78 (s, 3 H), 6.91−7.28 (m, 2 H), 8.31−8.41 (m, 1 H). − $^{13}C$ NMR ($CDCl_3$): δ = 23.00, 25.01, 29.30, 39.64, 69.1, 76.39, 83.02, 101.07, 104.67, 112.60 (d), 131.02 (d), 158.16, 162.07, 163.55, 167.24, 190.64. − EI MS; *m*/*z* (relative intensity): 361(7) [$M^+$], 318 (23), 290 (34), 253 (100), 238 (35), 228 (39), 175 (40), 146 (68), 140 (97). − $C_{19}H_{17}F_2NO_2S$ (361.41): calcd. C 63.14, H 4.74, F 10.51, N 3.88, O 8.85, S 8.87; found C 63.21, H 4.69, N 3.95.

**3h:** Purified by flash chromatography (*n*-hexane/EtOAc, 70:30). − White solid. − M.p. 122−124°C. − Yield 62%. − IR (KBr): $\tilde{\nu}$ = 3420 $cm^{-1}$, 2220, 1670, 1620, 695, 660. − $^1H$ NMR ($CDCl_3$): δ = 1.05 (t, 3 H, *J* = 7.3 Hz), 1.42 (s, 3 H), 1.77 (q, 2 H, *J* = 7.3 Hz), 2.66 (s, 3 H), 3.77 (s, 3 H), 6.85 and 7.70 (AA′-BB′ system, 4 H, *J* = 7.1 Hz). − $^{13}C$ NMR ($CDCl_3$): δ = 9.00, 28.45, 28.71, 29.03, 36.36, 55.46, 69.16, 78.20, 100.59, 114.42, 125.08, 128.47, 138.12, 140. 74, 162.46, 171.66, 190.61. − EI MS; *m*/*z* (relative intensity): 329 (30) [$M^+$], 300 (94), 258(100). − $C_{18}H_{19}NO_3S$ (329.41): calcd. C 65.63, H 5.81, N 4.25, O 14.57, S 9.73; found C 65.42, H 5.75, N 4.39.

**3i:** Purified by flash chromatography (*n*-hexane/EtOAc, 75:25). − White solid. − M.p. 143−144°C. −Yield 95%. − IR (KBr): $\tilde{\nu}$ = 2160 $cm^{-1}$, 1640, 760, 730. − $^1H$ NMR ($CDCl_3$): δ = 2.67 (s, 3 H), 3.88 (s, 3 H), 6.95−6.98 and 7.88−8.00 (AA′-BB′ system, 4 H, *J* = 6.9 Hz), 7.36−7.42 (m, 3 H), 7.59−7.64 (m, 2 H). − $^{13}C$ NMR ($CDCl_3$): δ = 29.04, 55.46, 84.40, 96.63, 114.44, 121.61, 125.17, 128.60, 128.84, 129.68, 131.82, 162.48, 171.73, 180.62. − EI MS; *m*/*z* (relative intensity): 333 (42) [$M^+$], 318 (20), 157 (100), 113 (53). − $C_{20}H_{15}NO_2S$ (333.40): calcd. C 72.05, H 4.53, N 4.20, O 9.60, S 9.62; found C 71.92, H 4.72, N 4.12.

**3j:** Purified by flash chromatography (*n*-hexane/EtOAc, 75:25). − Yellow solid; m.p. 163−164°C. − Yield 76%; IR (KBr): $\tilde{\nu}$ = 2200 $cm^{-1}$, 1670, 750. − $^1H$ NMR ($CDCl_3$): δ = 2.75 (s, 3 H), 2.83 (s, 3 H), 7.30−7.48 (m, 3 H), 7.58−7.85 (m, 2 H), 8.01 (s, 1 H). − $^{13}C$ NMR ($CDCl_3$): δ = 19.17, 29.20, 84.01, 96.50, 118.91, 121.47, 128.56, 129.67, 131.79, 147.78, 167.23, 190.56. − EI MS; *m*/*z* (relative intensity): 324 (68) [$M^+$], 309 (58), 157 (100), 113 (64), 83 (31), 69 (21). − $C_{17}H_{12}N_2OS_2$ (324.42): calcd. C 62.94, H 3.73, N 8.64, O 4.93, S 19.76; found C 63.12, H 3.69, N 8.92.

**Pyrido[3,4-*c*]thiazoles 4a−j. − General Procedures:** This is exemplified by the reaction of 5-acetyl-2-(4′-chlorophenyl)-4-ethynylphenylthiazole (**3d**) with dry ammonia. A solution of 5-acetyl-2-(4′-chlorophenyl)-4-ethynylphenylthiazole (**3d**) (0.260 g, 0.77 mmol) in dry ammonia and methanol ($NH_3$/MeOH 2 M, 8 mL) was heated at 120°C in a steel reactor for 12 h. The solvent was evaporated under reduced pressure. The residue was purified by flash chromatography eluting with a 90:10 *n*-hexane/EtOAc mixture to give **4d** (0.249 g, 96% yield).

**4a:** Purified by flash chromatography (*n*-hexane/EtOAc, 90:10). − White solid. − M.p. 220−222°C. − Yield 82%. − IR (KBr): $\tilde{\nu}$ = 1610 $cm^{-1}$, 780, 760. − $^1H$ NMR ($CDCl_3$): δ = 2.92 (s, 3 H), 7.48−7.52 (m, 3 H), 7.80 and 8.24 (AA′-BB′ system, 4 H, *J* = 8.2 Hz), 7.78−7.82 (m, 2 H), 8.11 (s, 1 H). − $^{13}C$ NMR ($CDCl_3$): δ = 29.70, 111.86, 125.92, 126.18, 126.28, 127.11, 128.21, 128.39, 128.96, 139.33, 152.71, 154.77, 160.23, 170.59; EI MS; *m*/*z* (relative intensity): 370 (100) [$M^+$], 185 (11), 158 (16), 114 (16), 113. − $C_{20}H_{13}F_3N_2S$ (370.38): calcd. C 65.03, H 3.27, F 15.43 N 7.58, S 8.68; found C 65.15, H 3.35, N 7.70.

**4b:** Purified by flash chromatography (*n*-hexane/EtOAc, 85:15). − White solid. − M.p. 100−102. − Yield 92%. − IR (KBr): $\tilde{\nu}$ = 1630 $cm^{-1}$, 1600, 1330, 790, 770. − $^1H$ NMR ($CDCl_3$): δ = 1.26 (t, 6 H), 2.87 (s, 3 H), 3.68 (q, 4 H), 5.63 (s, 1 H), 7.80 and 8.25 (AA′-BB′ system, 4 H, *J* = 8.4 Hz), 8.13 (s, 1 H). − $^{13}C$ NMR ($CDCl_3$):

δ = 15.24, 24.50, 62.22, 102.11, 112.98, 126.16, 128.24, 131.04, 133.74(q), 138.02, 152.57, 155.20, 159.70, 170.75, 175.57; EI MS; *m/z* (relative intensity): 396 (0.4) [M$^+$], 323 (100). − $C_{19}H_{19}F_3N_2O_2S$ (396.43): calcd. C 57.57, H 3.89, F 14.38 N 7.07, O 8.07, S 8.09; found C 57.46, H 3.79, N 7.18.

**4c:** Purified by flash chromatography (*n*-hexane/EtOAc, 90:10). − White solid. − M.p. 41−44°C. − Yield 90%. − IR (KBr): ṽ = 1610 cm$^{-1}$, 780, 760. − $^1$H NMR ($CDCl_3$): δ = 0.92 (t, 3 H), 1.25−1.58 (m, 8 H), 2.24 (t, 2 H), 2.89 (s, 3 H), 7.65 (s, 1 H), 7.79 and 8.24 (AA′-BB′ system, 4 H, *J* = 8.1 Hz). − $^{13}$C NMR ($CDCl_3$): δ = 14.11, 22.82, 24.74, 29.07, 29.71, 31.76, 38.33, 113.63, 126.13, 127.86, 128.34, 128.45, 128.88, 131.10 (q), 152.19, 159.47, 170.32. − EI MS; *m/z* (relative intensity): 378 (6) [M$^+$], 309 (100). − $C_{20}H_{21}F_3N_2S$ (378.46): calcd. C 65.47, H 5.59, F 15.06, N 7.40, S 8.47; found C 65.44, H 5.56, N 7.46.

**4d:** Purified by flash chromatography (*n*-hexane/EtOAc, 90:10).[13]

**4e:** Purified by flash chromatography (*n*-hexane/EtOAc, 80:10). − White solid. − M.p. 144−145°C. − Yield 74%. − IR (KBr): ṽ = 1590 cm$^{-1}$, 1580, 760, 740. − $^1$H NMR ($CDCl_3$): δ = 2.83 (s, 3 H), 7.23−7.49 (m, 6 H) 8.04−8.11 (m, 4 H), 8.14 (s, 1 H). − $^{13}$C NMR ($CDCl_3$): δ = 24.85, 111.54, 127.03, 127.84, 128.61, 128.75, 129.10, 131.88, 132.87, 139.46, 154.34, 160.27, 172.49. − EI MS; *m/z* (relative intensity): 302 (100) [M$^+$]. − $C_{19}H_{14}N_2S$ (302.39): calcd. C 75.47, H 4.67, N 9.26, S 10.60; found C 75.30, H 4.56, N 9.42.

**4f:** Purified by flash chromatography (*n*-hexane/EtOAc, 85:15). − Oil. − Yield 88%. − IR (neat): ṽ = 1580 cm$^{-1}$, 790, 760. − $^1$H NMR ($CDCl_3$): δ = 2.86 (s, 3 H), 7.04−8.08 (m, 9 H). − $^{13}$C NMR ($CDCl_3$): δ 28.67, 119.78, 124.15, 126.47, 127.35, 127.61, 130.40, 132.18, 151.14, 153.71. − EI MS; *m/z* (relative intensity): 308 (7) [M$^+$], 105 (100), 77 (61). − $C_{17}H_{12}N_2S_2$ (308.42): calcd. C 66.21, H 3.92, N 3.92, S 20.79; found C 65.96, H 3.80, N 3.78.

**4g:** Purified by flash chromatography (*n*-hexane/EtOAc, 80:20). − White solid. − M.p. 90−93°C. − Yield 75%; IR (KBr): ṽ = 3400 cm$^{-1}$, 1630, 740. − $^1$H NMR ($CDCl_3$): δ = 1.21−2.02 (m, 10 H), 2.76 (s, 3 H), 6.57−6.99 (m, 2 H), 7.78 (s, 1 H), 8.33−8.42 (m, 1 H). − $^{13}$C NMR ($CDCl_3$): δ = 21.24, 23.33, 24.64, 38.62, 71.88, 103.83, 108.48, 111.65 (d), 130.47 (d), 149.98, 157.57, 162.08, 166.52. − EI MS; *m/z* (relative intensity): 360 (5) [M$^+$], 317 (13), 228 (36), 175 (49), 146 (51), 105 (24), 77 (56). − $C_{19}H_{18}F_2N_2OS$ (360.42): calcd. C 63.32, H 5.03, F 10.54, O 4.4, N 7.77, S 8.90; found C 63.26, H 4.88, N 7.99.

**4h:** Purified by flash chromatography (*n*-hexane/EtOAc, 80:20). − Oil. − Yield 90%. − IR (neat): ṽ = 3480 cm$^{-1}$, 1600, 780. − $^1$H NMR ($CDCl_3$): δ = 0.79 (t, 3 H), 1.48 (s, 3 H), 1.68 (q, 2 H), 2.64 (s, 3 H), 3.87 (s, 3 H), 7.05 and 8.07 (AA′-BB′ system, 4 H, *J* = 7.1 Hz), 7.71 (s, 1 H); EI MS; *m/z* (relative intensity): 328 (2) [M$^+$], 313 (10), 299 (100). − $C_{18}H_{20}N_2O_2S$ (328.43).

**4i:** Purified by flash chromatography (*n*-hexane/EtOAc, 70:20). − White solid. − M.p. 154−155°C. − Yield 81%; IR (KBr): ṽ = 1590 cm$^{-1}$, 780, 760. − $^1$H NMR ($CDCl_3$): δ = 2.84 (s, 3 H), 3.86 (s, 3 H), 6.98 and 8.11 (AA′-BB′ system, 4 H, *J* = 10.9 Hz), 7.40−7.49 (m, 3 H), 8.02−8.06 (m, 3 H). − $^{13}$C NMR ($CDCl_3$): δ = 24.86, 55.48, 111.29, 114.46, 125.83, 127.04, 128.57, 128.75, 129.58, 139.59, 154.34, 162.65, 172.32; EI MS; *m/z* (relative intensity): 332 (100) [M$^+$]. − $C_{20}H_{16}N_2OS$ (332.42): calcd. C 72.26, H 4.85, O 4.81, N 8.43, S 9.64; found C 72.26, H 4.77, N 8.45.

**4j:** Purified by flash chromatography (*n*-hexane/EtOAc, 75:25). − White solid. − M.p. 170−172°C. − Yield 92%. − IR (KBr): ṽ = 1600 cm$^{-1}$, 1580, 790, 770, 750. − $^1$H NMR ($CDCl_3$): δ = 2.80 (s, 3 H), 2.88 (s, 3 H), 7.26−7.53 (m, 3 H), 8.05−8.14 (m, 4 H). − $^{13}$C NMR ($CDCl_3$): δ = 19.27, 24.90, 111.45, 114.49, 119.69, 127.08, 128.78, 129.75, 139.55, 154.43, 162.66, 167.26; EI MS; *m/z* (relative intensity): 323 (100) [M$^+$]. − $C_{17}H_{13}N_3S_2$ (323.43): calcd. C 63.13, H 4.05, N 12.29, S 19.82; found C 62.98, H 3.95, N 12.50.

**2-Substituted 5-Acetyl-4-aryl/heteroaryl/vinylthiazoles 5a−d. − General Procedures. − (a) Palladium-Catalysed Coupling of 2 with Organostannanes:** This is exemplified by the reaction of 5-acetyl-2-(4′-chlorophenyl)-4-thiazolyl triflate (**2b**) with 2-(tributylstannyl)thiophene. A mixture of 5-acetyl-2-(4′-chlorophenyl)-4-thiazolyl triflate (**2b**) (0.140 g, 0.36 mmol), 2-(tributylstannyl)thiophene (0.160 g, 0.43 mmol), LiCl (0.045 g, 1.08 mmol), and $Pd(PPh_3)_4$ (0.008 g, 0.007 mmol) in dioxane (4 mL) were treated under nitrogen at 90°C for 4 h. Then, the residue was purified by flash chromatography eluting with a 99:1 *n*-hexane/EtOAc mixture to give **5b** (0.110 g, 95% yield).

**5a:** Purified by flash chromatography (*n*-hexane/EtOAc, 95:5). − White solid. − M.p. 59−60°C. − Yield 90%. − IR (KBr): ṽ = 1690 cm$^{-1}$, 1490, 760. − $^1$H NMR ($CDCl_3$): δ = 2.54 (s, 3 H), 5.69 (d, 1 H, *J* = 2.23 Hz), 5.74 (d, 1 H, *J* = 2.23 Hz), 6.56 (dd, 1 H, *J* = 19.4 Hz), 7.26−7.60 (m, 3 H), 7.97−8.00 (m, 2 H). − $^{13}$C NMR ($CDCl_3$): δ = 31.39, 123.39, 126.97, 128.97, 129.21, 131.26, 132.62, 157.03, 168.96, 190.29. − EI MS; *m/z* (relative intensity): 229 (92) [M$^+$], 228 (100), 214 (28), 186 (30), 111 (36). − $C_{13}H_{11}NOS$ (229.05): calcd. C 68.11, H 4.84, N 6.11, O 6.98, S 13.96; found C 68.04, H 4.80, N 6.09.

**5b:** Purified by flash chromatography (*n*-hexane/EtOAc, 99:1). − White solid. − M.p. 118−119°C. − Yield 95%. − IR (KBr): ṽ = 1690 cm$^{-1}$, 1600, 1580, 800, 710. − $^1$H NMR ($CDCl_3$): δ = 2.52 (s, 3 H), 7.10−7.14 (m, 1 H), 7.39 and 7.90 (AA′-BB′ system, 4 H, *J* = 13.6 Hz) 7.48 (m, 1 H); 8.22 (m, 1 H). − $^{13}$C NMR ($CDCl_3$): δ = 31.04, 127.61, 128.14, 129.39, 129.63, 130.77, 131.00, 137.02, 152.13, 189.77. − EI MS; *m/z* (relative intensity): 319 (84) [M$^+$], 304 (82), 139 (100). − $C_{15}H_{10}ClNOS_2$ (319.82): calcd. C 56.33, H 3.15, Cl 11.09, N 4.38, O 5.00, S 20.05; found C 56.39, H 3.28, N 4.19.

**(b) Palladium-Catalysed Coupling of 2 with Arylboronic Acids:** This is exemplified by the reaction of 5-acetyl-2-phenyl-4-thiazolyl triflate (**2c**) with phenylboronic acid. To a solution of 5-acetyl-2-phenyl-4-thiazolyl triflate (**2c**) (0.252 g, 0.72 mmol) in $PhCH_3$ (6 mL), phenylboronic acid (0.182 g, 1.49 mmol), anhydrous potassium carbonate (0.150 g, 1.09 mmol), and tetrakis(triphenylphosphane)palladium(0) (0.016 g, 0.014 mmol) were added. The reaction mixture was gently purged with nitrogen and stirred at 90°C for 2 h under a nitrogen atmosphere. Then, EtOAc and saturated sodium bicarbonate were added; the organic layer was separated, washed with water, dried ($Na_2SO_4$), and concentrated at reduced pressure. The residue was purified by flash chromatography eluting with a 95:5 *n*-hexane/EtOAc mixture to give **5c** (0.150 g, 75% yield).

**5c:** Purified by flash chromatography (*n*-hexane/EtOAc, 95:5). − White solid. − M.p. 142−143°C. − Yield 75%. − IR (KBr): ṽ = 1665 cm$^{-1}$, 1525, 780, 760. − $^1$H NMR ($CDCl_3$): δ = 2.20 (s, 3 H), 7.42−7.50 (m, 6 H), 7.61−7.65 (m, 2 H), 7.98−8.03 (m, 2 H). − $^{13}$C NMR ($CDCl_3$): δ = 29.55, 126.46, 126.99, 128.42, 129.03, 129.28, 129.48, 131.27, 132.75, 134.93, 135.11, 159.15, 170.49, 191.79. − EI MS; *m/z* (relative intensity): 279 (100) [M$^+$], 264 (74), 140 (37), 133 (84). − $C_{17}H_{13}NOS$ (279.36): calcd. C 73.09, H 4.69, N 5.01, O 5.73, S 11.48; found C 73.12, H 4.71, N 4.97.

**5d:** Purified by flash chromatography (*n*-hexane/EtOAc, 75:25). − White solid. − M.p. 139−140°C. − Yield 93%. − IR (KBr): ṽ = 1710 cm$^{-1}$, 1670, 1510,770, 760. − $^1$H NMR ($CDCl_3$): δ = 2.22 (s, 3 H), 2.77 (s, 3 H), 7.53−7.71 (m, 3 H), 7.94 (s, 1 H) 8.04−8.09 (m, 1 H), 9.97 (s, 1 H). − $^{13}$C NMR (CDCl$_3$): δ = 19.16, 29.90, 118.81, 128.45, 129.76, 131.10, 133.52, 134.74, 135.73, 137.58, 147.87, 155.72, 164.73, 167.38, 189.97, 190.71. − EI MS; *m/z* (relative intensity): 328 (6) [M$^+$], 299 (80), 285 (100). − $C_{16}H_{12}N_2O_2S_2$ (328.03): calcd. C 58.53, H 3.69, N 8.54, O 9.75, S 19.49; found C 58.45, H 3.71, N 8.52.

**2-Substituted 5-Acetyl-4-carboxymethylthiazoles 5e−f. − General Procedures:** In a typical procedure a mixture of 5-acetyl-2-phenyl-4-thiazolyl triflate **2c** (0.315 g, 0.90 mmol) triethylamine (0.181 g, 1.80 mmol), palladium acetate (6 mg, 0.027 mmol), DPPF (15 mg, 0.027 mmol), and MeOH (0.72 mL, 18 mmol) in PhCH$_3$ (4 mL) was purged with carbon monoxide for 5 min and stirred under a CO balloon at 60°C for 8 h. Then, EtOAc and HCl 0.1 N were added; the organic layer was separated, washed with water, dried (Na$_2$SO$_4$), and concentrated at reduced pressure. The residue was purified by flash chromatography eluting with a 93:7 *n*-hexane/EtOAc mixture to give **5e** (0.153 g, 65% yield).

**5e:** Purified by flash chromatography (*n*-hexane/EtOAc, 93:7). − White solid. − M.p. 80−81°C. − Yield 65%. − IR (KBr): ṽ = 1690 cm$^{-1}$, 1670, 1510, 1240, 760. − $^1$H NMR (CDCl$_3$): δ = 2.65 (s, 3 H),4.03 (s, 3 H), 7.46−7.49 (m, 3 H), 7.95−8.00 (m, 2 H). − $^{13}$C NMR (CDCl$_3$): δ = 29.98, 53.20, 126.88, 127.12, 129.16, 131.68, 132.24, 140.83, 146.80, 163.20, 170.79, 191.23. − EI MS; *m/z* (relative intensity): 261 (100) [M$^+$], 246 (88), 218 (70), 121 (42), 115 (64), 104 (31). − $C_{13}H_{11}NO_3S$ (261.04): calcd. C 59.76, H 4.25, N 5.36, O 18.38, S 12.25; found C 59.78, H 4.27, N 5.40.

**5f:** Purified by flash chromatography (*n*-hexane/EtOAc, 85:15). − Yellow solid. − M.p. 182−185°C. − Yield 64%. − IR (KBr): ṽ = 1670 cm$^{-1}$, 1460, 1250; $^1$H NMR (CDCl$_3$): δ = 2.48 (s, 3 H), 2.77 (s, 3 H), 4.01 (s, 3 H), 8.03 (s, 1 H). − $^{13}$C NMR (CDCl$_3$): δ = 28.44, 30.46, 53.06, 107.04, 118.74, 128.83, 130.84, 148.09, 167.43, 171.39, 193.75. − EI MS; *m/z* (relative intensity): 82 (100) [M$^+$], 267 (75). − $C_{11}H_{10}N_2O_3S_2$ (282.33): calcd. C 46.80, H 3.57, N 9.92, O 17.00, S 22.71; found C 46.90, H 3.65, N 9.74.

**2-Substituted 5-Acetyl-4-aminothiazoles 5g−h. − General Procedures:** This is exemplified by the reaction of 5-acetyl-2-(4′-trifluoromethylphenyl)-4-thiazolyl triflate (**2a**) with morpholine. A mixture of 5-acetyl-2-(4′-trifluoromethylphenyl)-4-thiazolyl triflate (**2a**) (0.170 g, 0.43 mmol) and morpholine (0.223 g, 2.56 mmol) in PhCH$_3$ (4 mL) were treated at 90°C for 1 h. Then, the residue was purified by flash chromatography eluting with a 95:5 *n*-hexane/EtOAc mixture to give **5h** (0.136 g, 94% yield).

**5g:** Purified by flash chromatography (*n*-hexane/EtOAc, 85:15). − Yellow solid. − M.p. 71−72°C. − Yield 64%. − IR (KBr): ṽ = 1660 cm$^{-1}$, 1510, 760. − $^1$H NMR (CDCl$_3$): δ = 1.62 (m, 6 H), δ 2.37 (s, 3 H), 3.45 (m, 4 H), 7.18−7.35 (m, 3 H), 7.84−7.87 (m, 2 H). − $^{13}$C NMR (CDCl$_3$): δ = 24.34, 26.04, 30.25, 52.32, 110.87, 126.57, 128.90, 131.15, 133.09, 163.82, 166.12, 176.44. − EI MS; *m/z* (relative intensity): 286 (100) [M$^+$], 269 (80), 166 (97), 121 (68). − $C_{16}H_{18}N_2OS$ (286.03): calcd. C 69.56, H 2.92, N 10.15, O 5.79, S 11.58; found C 69.63, H 3.02, N 10.10.

**5h:** Purified by flash chromatography (*n*-hexane/EtOAc, 95:5). − Yellow solid. − M.p. 81−82°C. − Yield 94%. − IR (KBr): ṽ = 1670 cm$^{-1}$, 1635, 1530, 740. − $^1$H NMR (CDCl$_3$): δ = 2.50 (s, 3 H), 3.63 (m, 4 H), 3.88 (m, 4 H), 7.70 and 8.06 (AA′-BB′ system, 4 H, *J* = 8.3 Hz). − $^{13}$C NMR (CDCl$_3$): δ = 30.95, 51.01, 66.94, 111.70, 125.99, 126.06, 126.88, 135.91, 163.05, 165.93, 187.35. − EI MS; *m/z* (relative intensity): 356 (53) [M$^+$], 338 (53), 325 (41), 313 (55), 299 (64), 283 (38), 256 (52), 189 (78), 173 (100). − $C_{16}H_{15}F_3N_2O_2S$ (356.36): calcd. C 53.93, H 4.24, F 15.99, N 7.86, O 8.98, S 9.00; found C 53.49, H 4.05, N 7.93.

**5i:** A mixture of **2g** (0.100 g, 0.26 mmol), 4-methoxy-α-toluenthiol (0.207 g, 1.34 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.204 g, 1.34 mmol) in PhCH$_3$ (3 mL) were allowed to react at 90°C for 8 h. Then, the residue was purified by flash chromatography eluting with a 80:20 *n*-hexane/EtOAc mixture to give **5i** (0.070 g, 69% yield): White solid. − M.p. 131−132°C. − IR (KBr): ṽ = 1660 cm$^{-1}$, 1630, 790, 760. − $^1$H NMR (CDCl$_3$): δ = 2.51 (s, 3 H), 2.78 (s, 3 H), 3.79 (s, 3 H), 4.53 (s, 2 H), 6.83 and 7.36 (AA′-BB′ system, 4 H, *J* = 11.6 Hz), 7.96 (s, 1 H). − $^{13}$C NMR (CDCl$_3$): δ = 19.27, 29.95, 36.42, 55.26, 113.90, 118.40, 129.63, 130.29, 148.26, 158.80, 167.44, 189.31. − EI MS; *m/z* (relative intensity): 376 (46) [M$^+$], 343 (100). − $C_{17}H_{16}N_2O_2S_3$ (376.03): calcd. C 54.25, H 4.29, N 7.45, O 8.51, S 25.51; found C 54.31, H 4.27, N 7.43.

**5j:** A mixture of **2c** (0.202 g, 0.57 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.129 g, 0.86 mmol) were allowed to react in ethanol (10 mL) under reflux for 24 h. Then, EtOAc and HCl 0.1 N were added; the organic layer was separated, washed with water, dried (Na$_2$SO$_4$), and concentrated at reduced pressure. The residue was purified by flash chromatography eluting with a 90:10 *n*-hexane/EtOAc mixture to give **5j** (0.062 g, 44% yield): white solid. − M.p. 50−51°C. − IR (KBr): ṽ = 1680 cm$^{-1}$, 1630, 1220, 800, 740. − $^1$H NMR (CDCl$_3$): δ = 1.49 (t, 3 H, *J* = 7.2 Hz), 2.85 (s, 3 H), 4.62 (q, 2H, *J* = 7.2 Hz), 7.43−7.55 (m, 3 H), 7.91−7.97 (m, 2 H). − $^{13}$C NMR (CDCl$_3$): δ = 15.06, 29.71, 67.06, 114.63, 124.78, 126.37, 129.02, 131.41, 163.35, 169.93, 190.71. − EI MS; *m/z* (relative intensity): 247 (41) [M$^+$], 204 (21), 146 (50), 104 (100). − $C_{13}H_{13}NO_2S$ (247.31): calcd. C 63.14, H 5.30, N 5.66, O 12.94, S 12.96; found C 62.99, H 5.18, N 5.76.

**2-Substituted 5-Acetyl-thiazoles 6a−d. − General Procedures:** This is exemplified by the reduction reaction of 5-acetyl-2-(4′-chlorophenyl)-4-thiazolyl triflate **2b**. To a solution of 5-acetyl-2-(4′-chlorophenyl)-4-thiazolyl triflate **2b** (0.176 g, 0.45 mmol) (4 mL), tributylamine (0.32 mL), DPPF (0.015 g, 0.027 mmol), and Pd(OAc)$_2$ (0.006 g, 0.027 mmol) in PhCH$_3$, was added 99% formic acid (0.034 mL, 0.9 mmol). The reaction mixture was stirred at 90°C for 1 h under nitrogen. Then, EtOAc and 0.1 N HCl were added; the organic layer was separated, washed with water, dried (Na$_2$SO$_4$), and concentrated at reduced pressure. The residue was purified by flash chromatography eluting with a 97:3 *n*-hexane/EtOAc mixture to give **6d** (0.090 g, 85% yield).

**6a:** Purified by flash chromatography (*n*-hexane/EtOAc, 95:5). − White solid. − M.p. 150−151°C. − Yield 80%. − IR (KBr): ṽ = 1670 cm$^{-1}$, 760. − $^1$H NMR (CDCl$_3$): δ = 2.60 (s, 3 H), 7.27−7.50 (m, 3 H), 7.96−8.01 (m, 2 H), 8.33 (s, 1 H). − $^{13}$C NMR (CDCl$_3$): δ = 27.30, 127.00, 127.41, 128.13, 131.41, 132.82, 139.57, 146.13, 174.53, 190.13 . − EI MS; *m/z* (relative intensity): 203 (100) [M$^+$], 188 (87), 160 (79), 133 (11), 116 (17), 103 (25), 80 (9). − $C_{11}H_9NOS$ (203.04): calcd. C 65.01, H 4.47, N 6.90, O 7.88, S 15.75; found C 65.02, H 4.54, N 6.70.

**6b:** Purified by flash chromatography (*n*-hexane/EtOAc, 75:25). − White solid. − M.p. 114−115°C. − Yield 96%. − IR (KBr): ṽ = 1660 cm$^{-1}$, 1520. − $^1$H NMR (CDCl$_3$): δ = 2.60 (s, 3 H), 2.77 (s, 3 H), 7.93 (s, 1 H) 8.31 (s, 1 H. − $^{13}$C NMR (CDCl$_3$): δ = 19.20, 27.54, 118.35, 139.50, 167.23, 190.13. − EI MS; *m/z* (relative intensity): 224 (99) [M$^+$], 209 (100), 181 (81). − $C_9H_8N_2OS_2$ (224.30): calcd. C 48.19, H 3.60, N 12.49, O 7.13, S 28.59; found C 48.35, H 3.62, N 12.58.

**6c:** Purified by flash chromatography (*n*-hexane/EtOAc, 75:25). − White solid. − M.p. 100−101°C. − Yield 94%. − IR (KBr): ṽ = 1680 cm$^{-1}$, 760, 720. − $^1$H NMR (CDCl$_3$): δ = 2.63 (s, 3 H), 6.93−7.28 (m, 2 H), 8.28−8.35 (m, 1 H), 8.37 (s, 1 H). − $^{13}$C NMR (CDCl$_3$): δ = 23.72, 104.71, 105.23, 112.57 (d), 128.79, 130.63 (d), 158.07, 161.85, 163.17, 166.93, 190.34. − EI MS; *m*/*z* (relative intensity): 239 (91) [M$^+$], 224 (95), 196 (100). − $C_{11}H_7F_2NOS$ (239.02): calcd. C 55.23, H 2.95, F 15.90, N 5.86, O 6.69, S 13.38; found C 55.27, H 3.02, N 5.89.

**6d:** Purified by flash chromatography (*n*-hexane/EtOAc, 97:3). − White solid. − M.p. 148−149°C. − Yield 85%. − IR (KBr): $\tilde{\nu}$ = 1670 cm$^{-1}$, 820, 770. − $^1$H NMR (CDCl$_3$): δ = 2.61 (s, 3 H), 7.43 and 7.91 (AA′-BB′ system, 4 H, *J* = 8.8 Hz) 8.31 (s, 1 H). − $^{13}$C NMR (CDCl$_3$): δ = 27.01, 128.19, 129.41, 131.30, 137.54, 139.91, 146.10, 173.06, 190.03. − EI MS; *m*/*z* (relative intensity): 237 (99) [M$^+$], 222 (100), 194 (97), 137 (55). − $C_{11}H_8ClNOS$ (237.60): calcd. C 55.58, H 3.39, Cl 14.91, N 5.89, O 6.73, S 13.49; found C 55.45, H 3.41, N 6.05.

**Synthesis of 5-Hydrazono-2-phenyl-4-thiazolyl Triflate (7):** A mixture of **2c** (0.200 g, 0.57 mmol) and phenylhydrazine (0.129 g, 1.13 mmol) were allowed to react in DMSO (4 mL) at 60°C for 3 h. Then, EtOAc, and HCl 0.1 N were added; the organic layer was separated, washed with water, dried (Na$_2$SO$_4$), and concentrated at reduced pressure. The residue was purified by flash chromatography eluting with a 95:5 *n*-hexane/EtOAc mixture to give **7** (0.140 g, 56% yield). − Brown solid. − M.p. 118−122°C. − IR (KBr): $\tilde{\nu}$ = 3360 cm$^{-1}$, 1610, 740, 730. − $^1$H NMR ([D$_6$]DMSO): δ = 2.34 (s, 3 H), 6.62−6.95 (m, 10 H), 9.86 (s, 1 H). − $^{13}$C NMR (CDCl$_3$): δ = 12.51, 122.86, 125.87, 128.58, 128.65, 129.03, 132.38, 167.37, 170.24. − EI MS; *m*/*z* (relative intensity): 441 (16) [M$^+$], 308 (26), 177(100), 136 (44). C 55.27, H 3.02, N 6.06. − $C_{18}H_{14}F_3N_3O_3S_2$ (441.04): calcd. C 48.97, H 3.20, F 12.92, N 9.52, O 10.88, S 14.50; found C 48.91, H 3.22, N 6.57.

**Synthesis of Pyrazolo[3,4-*d*]thiazole (8):** A mixture of **2c** (0.200 g, 0.57 mmol) and phenylhydrazine (0.129 g, 1.13 mmol) were allowed to react in PhCH$_3$ (6 mL) at 90°C for 12 h. Then, EtOAc and HCl 0.1 N were added; the organic layer was separated, washed with water, dried (Na$_2$SO$_4$), and concentrated at reduced pressure. The residue was purified by flash chromatography eluting with a 97:3 *n*-hexane/EtOAc mixture to give **8** (0.042 g, 32% yield). − Oil. − IR (neat): $\tilde{\nu}$ = 1600 cm$^{-1}$, 720. − $^1$H NMR (CDCl$_3$): δ = 1.18 (s, 3 H), 7.15−7.31 (m, 10 H), 9.86. − $^{13}$C NMR (CDCl$_3$): δ = 30.39, 115.81, 118.57, 125.43, 125.82, 128.48, 128.58, 141.12. − EI MS; *m*/*z* (relative intensity): 293 (2) [(M + 2)$^+$], 291 (1) [M$^+$], 278 (100), 201 (58), 194 (30), 149 (26), 135 (23), 119 (22), 105 (66). − $C_{17}H_{13}N_3S$ (291.04).

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