Pyrido[3,4-*c*]Thiazoles through Combined Palladium-Catalysed Coupling of 2-Substituted-5-acetyl-4-thiazolyltriflates with Alkynes/Annulation Reactions

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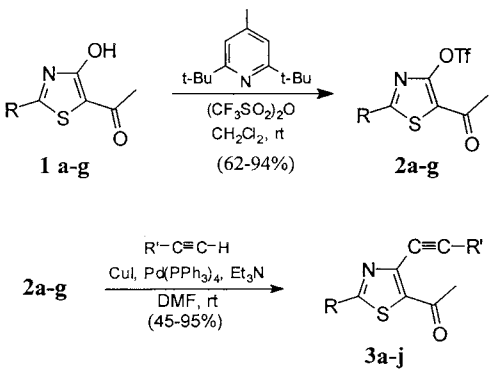
2-Substituted-5-acetyl-4-thiazolyltriflates give in good yields functionalised pyrido[3,4-*c*]thiazoles through combined palladium-catalysed coupling with 1-alkynes/6-*endo-dig* annulation reactions in the presence of ammonia.

The presence of the thiazole moiety in the structures of several naturally occurring molecules with important antibiotic, endothelin converting enzyme inhibitor, anti-tumor, and immunosuppressive properties, continues to spur intensive synthetic efforts regarding their acquisition.[1] *In vitro* cytotoxicity of a large number of condensed thiazoles has been tested against several cell lines.[2]

We have recently focused our attention on the synthesis of 2-substituted-5-acetyl-4-hydroxythiazoles **1** by the reaction between conjugated azoalkenes and thioamides and removal of NH-BOC-hydrazo protecting group.[3]

In connection with our ongoing interest in developing new synthetic strategies for the construction of heterocyclic rings involving alkyne derivatives,[4] we thought that the 2-substituted-5-acetyl-4-thiazolyltriflates **2** (Scheme 1) could represent the starting building block for the synthesis of functionalised condensed thiazoles.

Although some reports of palladium-catalysed coupling reactions of halothiazoles and 2-halo-Δ^2-thiazolines have appeared in the literature,[5] no examples of palladium-catalysed coupling exist for thiazolyltriflates. In the last years the application of aryl/heteroaryl and vinyl triflates has broadened enormously. We assumed that the choice of the trifluoromethanesulfonate[6] as leaving group is a key point to obtain fruitful results for the introduction of a functionalised carbon-side chain into these heteroaromatics.



Scheme 1.

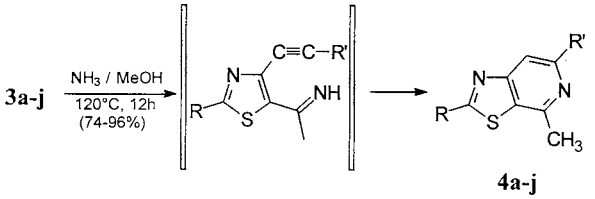
Table 1. 4-Alkynylthiazoles **3**, and pyrido[3,4-*c*]thiazoles **4**

Recovered **3** / % yield[a]	Recovered **4** / % yield[a]
3a / 62	**4a** / 82
3b / 56	**4b** / 92
3c / 55	**4c** / 90
3d / 78	**4d** / 96
3e / 82	**4e** / 74
3f / 87	**4f** / 88
3g / 67	**4g** /75
3h / 45	**4h** /90
3i /95	**4i** / 81
3j / 76	**4j** /92

[a] % Yields referred to single runs and are for pure and isolated products.

Indeed the triflates **2a-g**, easily prepared in good to high yields (62-94%) from 2-substituted-5-acetyl-4-hydroxythiazoles under usual reaction conditions,[7] undergo palladium-catalysed coupling with 1-alkynes,[8] at room temperature, to afford the 2-substituted-5-acetyl-4-alkynylthiazoles **3a-j** (45-95% yield) (Scheme 1 and Table 1).

The subsequent treatment of **3a-j** with ammonia in MeOH leads to the formation of the pyrido[3,4-*c*]thiazoles[9] **4a-j** (Scheme 2 and Table 1) in excellent yields (74-96%) through sequential addition/elimination/cycloammination reactions.[10] The reaction mechanism probably involves the formation of an imine[11] that undergoes a regioselective 6-*endo-dig* cyclization to give **4**.



4a-j

Scheme 2.

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/cycloammination of 4-pentynones gave 2,3,5-substituted pyrroles and fused pyrrole systems,[10] while the presence of γ-ketoalkyne moiety in an aromatic framework is responsible for the 6-*endo-dig* cyclization.

In conclusion the combined palladium-catalysed coupling of the easily obtainable 2-substituted-5-acetyl-4-thiazolyltriflates with alkynes/6-*endo-dig* annulation reactions in the presence of ammonia represents a simple and efficient method for the preparation of functionalised pyrido[3,4-*c*]thiazoles.

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8 Synthesis of **3e**, general procedure: to a solution of 2-phenyl-5-acetyl-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(triphenylphosphine) palladium(0) (0.045 g, 0.038 mmol) 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); mp 165-166 °C; ^{1}H NMR ($CDCl_3$) δ 8.03-7.26 (m, 10 H), 2.86 (s, 3 H);^{13}C NMR ($CDCl_3$) δ 190.6, 171.7, 141.6, 139.5, 132.2, 131.7, 129.6, 128.5, 127.0, 121.4, 96.7, 84.0, 29.6; Ms *m/e* 303 (M^+, 34), 288 (25), 157 (100), 121 (50), 113 (62), 105 (15), 77 (9).

9 Synthesis of **4d**, general procedure: a solution of 2-(4'-chlorophenyl)-4-ethynylphenyl-5-acetylthiazole **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); mp 175-177 °C; ^{1}H NMR ($CDCl_3$) δ 8.04-7.39 (m, 10 H), 2.74 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.0, 159.1, 153.4, 151.3, 138.2, 137.0, 138.5, 128.3, 128.1, 127.9, 127.7, 127.3, 126.0, 110.4, 28.3; Ms *m/e* 336 (M^+, 100).

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