SYNTHESIS OF 3-ARYL-5-R-THIO-[1,3]THIAZOLO[4',5':4,5]PYRIMIDO-[1,6-*a*]BENZIMIDAZOLE-2(3*H*)-THIONES

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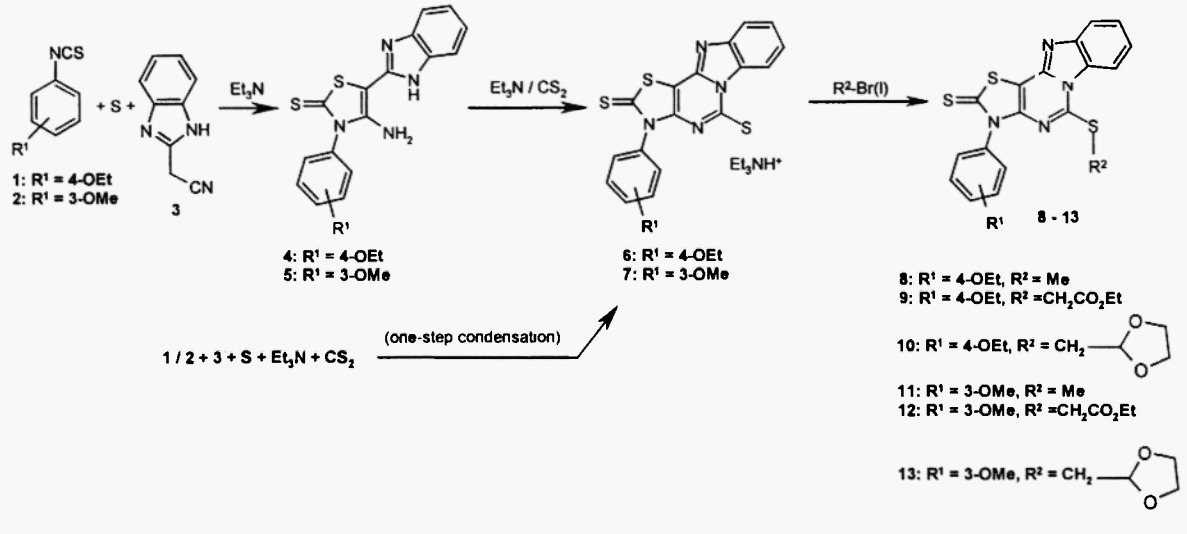
Abstract: A new five-component condensation of isothiocyanates, sulfur, 2-cyanomethylbenzimidazole, triethylamine and carbon disulfide furnishes triethylammonium 3-aryl-[1,3]thiazolo[4',5':4,5]pyrimido[1,6-*a*]benzimidazole-2(3*H*)-thioxo-5-thiolates, the alkylation of which gives 3-aryl-5-R-thio-[1,3]thiazolo[4',5':4,5]pyrimido[1,6-*a*]benzimidazole-2(3*H*)-thiones.

Pyrimidinothiazole derivatives are of a pharmacological potential. In particular, they possess antiinflammatory[1], antimicrobial[2], fungicidic[3], antiblastomic[2,4] and antiviral[2] activities. We have synthesized new 3-aryl-5-R-thio-[1,3]thiazolo[4',5':4,5]pyrimido[1,6-*a*]benzimidazole-2(3*H*)-thiones **8-13.** In the first step, condensation[5,6] of isothiocyanates **1**, **2** with sulfur and 2-cyanomethylbenzimidazole **3** in DMF in the presence of triethylamine furnished 4-amino-1,3-thiazole-2(3*H*)-thiones **4, 5**.[7,8] Then, cyclization of **4, 5** in the presence of carbon disulfide and triethylamine gave [1,3]thiazolo[4',5':4,5]pyrimido[1,6-*a*]benzimidazole-2(3*H*)-thione-5-thiolates **6, 7**.[7,9] In the third step, compounds **6, 7** were alkylated to give the desired products **8-12**.[7,10]



This report pertains to a greatly simplified synthesis of salts **6, 7** by a hitherto unknown one-pot condensation of aryl isothiocyanate **1** or **2**, **3**, sulfur, and carbon disulfide in the presence of triethylamine.[11] Since this reaction and the subsequent alkylation of **6**, **7** to give **8-13** are highly efficient, this methodology is suitable for combinatorial synthesis.

References and Notes

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7. The structures of new compounds **4-13** were fully consistent with the ^{1}NMR and MS data.
8. Synthesis of **4**, **5**: A solution of **1** or **2**, **3**, and sulfur (0.01 mol each) in DMF (3 ml) was stirred and treated with Et_3N (1.5 ml). The mixture was stirred and heated to 60 °C for 1 h, and then poured into water. The resultant precipitate was filtered and crystallized from DMF/i-PrOH. Compound, yield, mp: **4**, 73%, 273-274 °C; **5**, 70%, 226-227 °C.
9. Cyclization of **4**, **5**: A mixture of **4** or **5** (2 g), Et_3N (2 ml), and carbon disulfide (2 ml) was heated under reflux and treated dropwise with DMF until a solution was formed. The solution was heated under reflux for 1.5 h, then cooled, concentrated under a reduced pressure, and the residue was treated with EtOH (10 ml). The resultant product **6** or **7** was crystallized from DMF/EtOH.
10. Alkylation of **6**, **7**: Compound 6 or **7** (0.5 mmol) in DMF (3 ml) was allowed to react with an alkylating agent for 1h under the temperature conditions given below. Then the mixture was treated with water (50 ml), and the resultant precipitate was crystallized from DMF/EtOH. Reagents, reaction temperature, product, yield, mp: **6** and Mel, 23 °C, **8**, 73%, 225-226 °C; **6** and $BrCH_2CO_2Et$, 50 °C, **9**, 82%, 209-210 °C; **6** and 1,3-dioxolan-2-ylmethyl bromide, reflux, **10**, 74%, 210-211 °C; **7** and Mel, 23 °C, **11**, 77%, 259-260 °C; **7** and $BrCH_2CO_2Et$, 50 °C, **12**, 84%, 212-213 °C; **7** and 1,3-dioxolan-2-ylmethyl bromide, reflux, **13**, 73%, 167-168 °C.
11. One-pot synthesis of **6**, **7**: A solution prepared from **1** or **2**, sulfur, **3** (0.1 mol each), DMF (3 ml), Et_3N (1.5 ml), and CS_2 (1.5 ml) in the order indicated was allowed to stand at 23 °C for 1.5 h and then worked up as described above. Compound, yield, mp: **6**, 81%, 219-220 °C; **7**, 86%, 199-200 °C.

Received on June 10, 2002