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 antiinflammatory¹, antimicrobial², fungicidal³, antitumor^{2,4} and antiviral² 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**.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

1. E.R. El-Bendary, M.A. El-Sherbeny, F.A. Badria, *Bull. Chim. Farm.* **137**, 115 (1998)
2. N.S. Habib, S.M. Rida, E.A.M. Badawey, H.T.Y. Fahmy, *Monatsh. Chem.* **127**, 1209 (1996)
3. M.A. El-Sherbeny, F.A. Badria, S. Kheira, *Med. Chem. Res.* **6**, 28 (1996)
4. M.B. Devani, C.J. Shishoo, U.S. Pathak, S.H. Parikh, A.V. Radhakrishnan, A. Padhya, C. *Arzneim.-Forsch.* **27**, 1652 (1977)
5. V.K. Gewald, *Journal für praktische Chemie.* **32**, 26 (1966)
6. E.S.A.M. Badawey, A.A. Hazzaa, S.M. Rida, H.T.Y. Fahmy, *Arch. Pharm. (Weinheim, Ger.)* **325**, 565 (1992)
7. The structures of new compounds **4-13** were fully consistent with the ¹NMR 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 Et₃N (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), Et₃N (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 1 h 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 MeI, 23 °C, **8**, 73%, 225-226 °C; **6** and BrCH₂CO₂Et, 50 °C, **9**, 82%, 209-210 °C; **6** and 1,3-dioxolan-2-ylmethyl bromide, reflux, **10**, 74%, 210-211 °C; **7** and MeI, 23 °C, **11**, 77%, 259-260 °C; **7** and BrCH₂CO₂Et, 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), Et₃N (1.5 ml), and CS₂ (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.

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