3-芳基/芳氧甲基-6-芳基-1,2,4-三唑并[3,4-b]-1,3,4-噻二唑衍生物的合成及生物活性

史海健,王忠义[1],史好新

(安徽师范大学化学系,芜湖 241000;[1] 中国科技大学化学系,合肥 230026)

噻二唑类杂环化合物有广泛的生物活性,如消炎、驱虫、除草、调节植物生长、防止水稻白叶枯病、柑桔溃疡病、蕃茄青枯病等[1~3]。而1,2,4-三唑类杂环化合物也有相当广泛的生物活性,如抗菌、抗痉挛、消炎、抗血小板凝聚及调节植物生长等[4~6]。如果合成既含有1,2,4-三唑环,又含有1,3,4-噻二唑环的新型稠杂环化合物,同时改变取代基,有可能产生新的生物活性,这对于寻找新药和探索构效关系,有一定的意义。本文研究了3-芳基/芳氧甲基-4-氨基-5-巯基-1,2,4-三唑和羧酸在三氯氧磷作用下合成的16个新的化合物及其生物活性。并研究了反应温度对反应产率的影响。结果表明,有些化合物有较强的生物活性。所有化合物均经元素分析、红外光谱、核磁共振氢谱和质谱鉴定其结构。

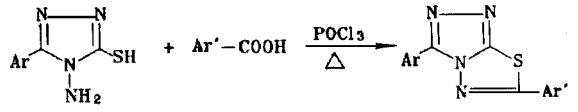
实 验 部 分

X_4型显微熔点测定仪测定熔点,温度未校正;元素分析仪为PE-2400型;红外光谱用FTS-40型红外光谱仪(美国Bio-rad公司)测定,KBr压片;^{1}HNMR用EM-360,60 MHz核磁共振仪测定,TMS为内标;MS用HP5989A型质谱仪测定。试剂一般为分析纯或化学纯。

1 3-芳基-4-氨基-5-巯基-1,2,4-三唑的合成

参考文献[7]合成。

2 3a~i的合成(图1)



Ar-:3a~g:β-Py-;3h~i:Ph-;3j~p:PhOCH$_2$-.

Ar′-:3a,3h:3,4-(CH$_3$)$_2$C$_6$H$_3$-;3b:3-CH$_3$C$_6$H$_4$-;3c:3,4-(HO)$_2$C$_6$H$_3$-;3d:o-O$_2$NC$_6$H$_4$-;3e:m-O$_2$NC$_6$H$_4$-;3f:p-O$_2$NC$_6$H$_4$-;3g,3i,3m:3-O$_2$N-p-ClC$_6$H$_3$-;3j:α-C$_{10}$H$_7$-;3k:3,4-(CH$_3$O)$_2$C$_6$H$_3$-;3l:o-ClC$_6$H$_4$-;3n:β-Py-;3o:p-H$_2$NC$_6$H$_4$-;3p:Ph-CH=CH-.

Fig 1 Route of synthesis of compounds **3a~i**.

将**1**(3 mmol)放入园底烧瓶中,再加入**2**(3.5 mmol)及$POCl_3$ 5 ml,在(95~98)℃搅拌反应(4~6) h。然后减压蒸去过量的$POCl_3$,剩余物倒入50 ml冰水中,搅拌、静置、抽滤,用10%NaOH溶液洗涤反应产物,再用水洗至中性,干燥得粗产品,在乙醇中重结晶得纯品。**3a**,产率43%,mp 120~122℃;**3b**,产率45%,mp 101~102.5℃;**3c**,产率38%,mp 236~238℃;**3d**,产率46%,mp 208~210℃;**3e**,产率45%,mp 178~180℃;**3f**,产率51%,mp 248~250℃;**3g**,产率52%,mp 282~284℃;**3h**,产率36%,mp 159~160℃;**3i**,产率42.6%,mp 226~228℃。

3 1′的合成[8~10](图2)

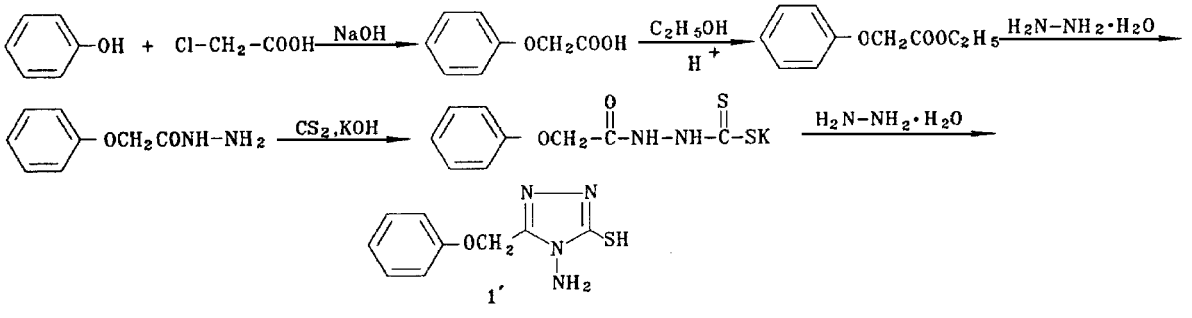


Fig 2 Route of synthesis of compound **1′**.

4 3j~p的合成

1′与羧酸的反应合成**3j~p**与前法相同。**3j**,产率85.20%,mp 139~141℃;**3k**,产率90.6%,

收稿日期:1998-02-05

基金项目:安徽省自然科学基金和安徽省教委科学基金资助项目

Tel:(0553)3869920(H)

mp 171 ~171.5 ℃; **3l**,产率 83.5 %, mp 88 ~90 ℃; **3m**,产率 77.5 %, mp 87 ~89 ℃; **3n**,产率 35.1 %, mp 103 ~105 ℃; **3o**,产率 34.4 %, mp 190 ℃(dec.); **3p**,产率 49.9 %, mp 141 ~143 ℃。

结 果 与 讨 论

元素分析的实验值与计算值虽有一定误差,但均在允许范围内;核磁共振氢谱与各化合物的结构相符合;质谱的分子离子峰均出现,有的为基峰,说明这类化合物较稳定。

生物活性 用平皿试验法,以青霉素、庆大霉素和链霉素为参比,药液浓度为 0.002 %,研究了这些化合物对金黄色葡萄球菌(G^+)、大肠杆菌(G^-)和枯草芽胞杆菌的抑菌作用。结果表明,**3b**和**3g**对 3 种菌都有较强的抑菌活性;**3c**,**3h**,**3j**,**3k**,**3n**和**3o**对金黄色葡萄球菌有较强的抑菌活性;**3a**对大肠杆菌有较强抑菌作用;**3a**,**3h**,**3i**,**3k**,**3n**,**3o**对枯草芽胞杆菌有较强抑菌作用。其余对 3 种菌的抑菌作用都较弱。

关键词 3,6-二芳基-1,2,4-三唑并[3,4-*b*]-1,3,4-噻二唑;合成;生物活性

参 考 文 献

1 Dahle Norman, A. 3-Benzyl-2-methylimine-5-phenyl-Δ^4-1,3,4-thiadiazolines for combationg undesired plant growth, U.S. 4,104,053, 1979 (C.A. 1979, **90**: 103962c)

2 Velsicol. Thiadiazolylimidazolinones. Chemical Corp., Austrian, 345,816, 1979 (C.A. 1979, **90**: 121604s)

3 张自义,杨虎.酰氨基硫脲及其杂环衍生物研究 II.1-[5-(α-萘)-2H-四唑-2-乙酰]-4-苯基硫脲及其相关杂环衍生物的合成.有机化学,1986,**3**: 184

4 Chaaban I, Oji OO. Synthesis and preliminary antibacterial activity of 3-(2-arylamino-1,3,4-thiadiazol-5-yl)-4-hydroxy-4′-substituted. *J Indian Chem Soc*, 1984, **61**: 523

5 Omar A, Mohsen ME, Aboulwata OM, *et al*. Synthesis and anticonvulsant properties of a novel series of 2-(substituted amino)-5-aryl-1,3,4-oxadiazole derivatives. *J Heterocycl Chem*, 1984, **21**: 1415

6 Clemence F, Joliveau C, Fouranx R. *et al*. 4H-1,2,4-Triazole derivatives and their use as medicines. C.A. 1985, **102**: 95677n

7 张自义,李明,赵岚,等.3-烷基/芳基-6-(3′-吡啶基均三唑并[3,4-*b*]-1,3,4-噻二唑类化合物的合成.有机化学,1993,**13**: 397

8 Wang ZY, Shi HJ, Shi HX, *et al*. The synthesis of aryloxy-carboxylic acid under microwave, solid base as a support. *Chin Chem Letters*, 1996, **7**: 527

9 史海健,王忠义,史好新.微波辐射下的芳基甲酰氨基硫脲的合成.有机化学,1996,**16**: 242

10 王忠义,史海健,史好新.微波炉加热法合成 3-芳基-1,2,4-三唑啉-5-硫酮.有机化学,1997,**17**: 271

SYNTHESIS AND BIOLOGICAL ACTIVITIES OF DERIVATIVES OF 3-ARYL/ARYLOXYMETHYL-6-ARYL-1,2,4-TRIAZOLO[3,4-*B*]-1,3,4-THIADIAZOLES

Shi Haijian (Shi HJ), Wang Zhongyi (Wang ZY)[1] and Shi Haoxin (Shi HX)

(*Department of Chemistry, Anhui Normal University, Wuhu 241000;*
[1] *Department of Chemistry, The University of Science and Technology of China, Hefei 230026*)

ABSTRACT **AIM:** To synthesize a number of novel heterocyclic compounds and screen for their biological activities. Sixteen title compounds were prepared. **METHODS:** These novel compounds were prepared by the reaction of 3-aryl/aryloxymethyl-4-amino-5-mercapto-1,2,4-triazoles with aryl carboxylic acids in the presence of phosphorus oxychloride. The structures of these compounds were confirmed by elemental analysis, IR, ^{1}HNMR and MS. The reaction conditions for the synthesis had been investigated. All the compounds were screened for antimicrobial activity against bacteria *S. aureus*, *E. coli* and *B. subilis*. The concentration of the test compounds was 0.002 %. The antibacterial activities of the test compounds were compared with those of penicillin and gentamicin. **RESULTS:** The results display that some of them possess strong biological activities. **CONCLUSION:** Syntheses of these novel heterocyclic compounds and study on their biological activities are very important and valuable in medicine.

KEY WORDS 3,6-diaryl-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles; synthesis; biological activity