Monatshefte für Chemie 134, 837–841 (2003)
DOI 10.1007/s00706-002-0557-9

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

A Convenient Procedure for the Formation of 2-Substituted Thiazolopyridines

Gamal A. El-Hiti*

Department of Chemistry, Faculty of Science, Tanta University, Tanta 31527, Egypt

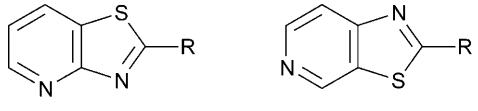
Received August 26, 2002; accepted (revised) September 9, 2002
Published online February 3, 2003

Summary. 2-Substituted thiazolo[4,5-*b*]pyridines and thiazolo[5,4-*c*]pyridines are prepared in reasonable yields by a procedure involving reaction of a mixture of *ortho*-amino (diisopropyldithiocarbamato) pyridine, carboxylic acid, and phosphorus oxychloride. The procedure provides a more convenient route than methods involving prior formation and isolation of the acid amide and cyclisation to give the desired product. The procedure is proven to be general for a wide range of substituents.

Keywords. Thiazolopyridines; Carboxylic acids; Phosphorus oxychloride; Amino (diisopropyldithiocarbamato) pyridines; Cyclisation.

Introduction

Derivatives of thiazolopyridine have been reported to exhibit various biological activities including analgesic, antipyretic, anti-inflammatory, and antifungal effects [1–4]. Therefore, the synthesis of such heterocyclic ring systems is attractive. In the last few years a number of methods has been developed for the synthesis of thiazolopyridines [5–11]. As part of our own interests [12], recently, we have developed a novel approach to various heterocyclic compounds [13]. In the present work we report a convenient procedure for the synthesis of 2-substituted thiazolo[4,5-*b*]pyridines (**1**) and 2-substituted thiazolo[5,4-*c*]pyridines (**2**).



1 **2**

Fig. 1. Compounds **1** and **2**

* E-mail: gelhiti@yahoo.co.uk
Present address: Centre for Clean Chemistry, Department of Chemistry, University of Wales Swansea, Swansea, SA2 8PP, UK

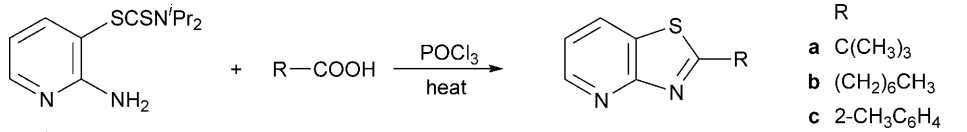
Results and Discussion

Synthesis of **1** and **2** usually involves treatment of *ortho*-aminochloropyridines with a thioester in alkaline medium, followed by acid treatment [6]. However, this method has not been widely applied and no simple 2-substituted thiazolopyridines have been prepared. Moreover, it involves three steps and usually gives moderate yields which considerably limits its scope. An attractive alternative approach involves treatment of *ortho*-amino (diisopropyldithiocarbamato) pyridine with acid chloride in the presence of base to produce the corresponding acid amide, followed by acid treatment to afford 2-substituted thiazolopyridines [10, 11]. This method has been widely applied and usually gives excellent yields. Whilst such a method can be quite efficient and convenient, it suffers from the poor availability and stability of appropriately substituted acid chlorides. Moreover, it involves an extra step to prepare the acid chloride. This prompted us to investigate a novel approach in which *ortho*-amino (diisopropyldithiocarbamato) pyridine (**3**) or (**4**) and the carboxylic acid were treated *in-situ* with phosphorus oxychloride.

2-Amino-3-(diisopropyldithiocarbamato) pyridine (**3**) and 4-amino-3-(diisopropyldithiocarbamato) pyridine (**4**) were prepared according to literature procedures [10, 11]. Thus, mixture of **3** and 2,2-dimethylpropionic acid in phosphorus oxychloride was heated under reflux and after work-up 2-*tert*-butylthiazolo[4,5-*b*] pyridine (**1a**) was isolated. A series of experiments was conducted in which the reaction conditions were varied in an attempt to improve the yield of the desired product. It was found that the optimum yield was obtained when the reaction mixture of **3** (1.0 molar equivalents), carboxylic acid (1.2 molar equivalents), and phosphorus oxychloride (5 cm^3) was refluxed for 4 h. The procedure is proven to be general for a wide variety of carboxylic acids (pivaloic, octanoic, 2-toluic, 4-toluic, 2-chlorobenzoic, 4-chlorobenzoic, 4-anisic, and 3-nitrobenzoic acid) to produce **1** (Scheme 1) in 58–70% yields.

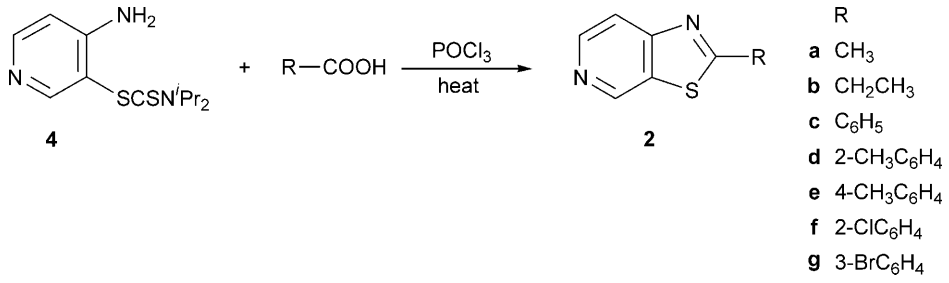
The structures of compounds **1** were confirmed by ^{1}H NMR, ^{13}C NMR, mass spectra, and high resolution mass spectral data and found to be identical with those published already [10, 11, 14].

In the same way as described for **3**, **4** was reacted with carboxylic acid (acetic, propanoic, benzoic, 2-toluic, 4-toluic, 2-chlorobenzoic, and 3-bromobenzoic acid) in phosphorus oxychloride. Indeed, various 2-substituted thiazolo[5,4-*c*]pyridines (**2**) (Scheme 2) were obtained in reasonable yields (54–71%).



R
a $C(CH_3)_3$
b $(CH_2)_6CH_3$
c 2-$CH_3C_6H_4$
d 4-$CH_3C_6H_4$
e 2-ClC_6H_4
f 4-ClC_6H_4
g 4-$CH_3OC_6H_4$
h 3-$O_2NC_6H_4$

Scheme 1



Scheme 2

The structures of compounds **2** were confirmed by ^{1}H NMR, ^{13}C NMR, mass spectra, and accurate mass spectral data which were in agreement with the compounds published before [10, 11, 14].

In conclusion, the reaction accommodates a wide range of substituents (aliphatic and aromatic) in the thiazole ring. Therefore, it represents a useful new procedure for the formation of 2-substituted thiazolopyridines.

Experimental

Melting points (uncorrected) were determined on an electrothermal melting MEL-TEMP II apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Low-resolution mass spectra were recorded on a Quattro II triple quadrupole mass spectrometer (electron impact: 70 eV; chemical ionization: ammonia). Accurate mass data were obtained on a MAT 900 instrument. Column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). Compounds **3** and **4** were prepared according to the method described in Refs. [10, 11]. Their analytical data agreed with the published ones.

General Procedure for the Formation of 2-Substituted Thiazolopyridines **1** *and* **2**

The appropriate carboxylic acid (3.6 mmol) and 0.81 g of *ortho*-amino (diisopropydithiocarbamato)-pyridine (3.01 mmol) were dissolved in 5 cm^3 of $POCl_3$. The mixture was refluxed for 4 h, then cooled, and made alkaline with ice-cold NaOH solution. It was extracted with 2 × 15 cm^3 of ethyl acetate and the organic layers were washed with 2 × 15 cm^3 of H_2O. The combined aqueous layers were extracted once with 15 cm^3 of ethyl acetate and the organic extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by flash column chromatography using diethyl ether:light petroleum (b.p.: 30–40°C) = 1:1 as eluent to give the pure 2-substituted thiazolopyridines.

2-tert-Butylthiazolo[4,5-b]pyridine (**1a**)

Yield: 66%; mp: 78–79°C (Ref. [10] 78°C).

2-Heptylthiazolo[4,5-b]pyridine (**1b**)

Yield: 62%; mp: 57–58°C (Ref. [10] 57–58°C).

2-(o-Tolyl)thiazolo[4,5-b]pyridine (**1c**)

Yield: 61%; mp: 90–91°C (Ref. [10] 90–90.5°C).

2-(p-Tolyl)thiazolo[4,5-b]pyridine (**1d**)

Yield: 63%; mp: 135–136°C (Ref. [10] 135–136°C).

2-(2-Chlorophenyl)thiazolo[4,5-b]pyridine (**1e**)

Yield: 62%; mp: 122–123°C (Ref. [10] 122°C).

2-(4-Chlorophenyl)thiazolo[4,5-b]pyridine (**1f**)

Yield: 70%; mp: 186°C (Ref. [10] 185–186°C).

2-(4-Methoxyphenyl)thiazolo[4,5-b]pyridine (**1g**)

Yield: 64%; mp: 143°C (Ref. [10] 142°C).

2-(3-Nitrophenyl)thiazolo[4,5-b]pyridine (**1h**)

Yield: 58%; mp: 224–226°C (Ref. [10] 225–227°C).

2-Methylthiazolo[5,4-c]pyridine (**2a**)

Yield: 64%; mp: 94–95°C (Ref. [11] 94–95°C).

2-Ethylthiazolo[5,4-c]pyridine (**2b**)

Yield: 71%; mp: 41°C (Ref. [11] 40°C).

2-Phenylthiazolo[5,4-c]pyridine (**2c**)

Yield: 59%; mp: 135–136°C (Ref. [11] 135–136°C).

2-(o-Tolyl)thiazolo[5,4-c]pyridine (**2d**)

Yield: 60%; mp: 78–79°C (Ref. [11] 77–78°C).

2-(p-Tolyl)thiazolo[5,4-c]pyridine (**2e**)

Yield: 66%; mp: 143–144°C (Ref. [11] 143°C).

2-(2-Chlorophenyl)thiazolo[5,4-c]pyridine (**2f**)

Yield: 61%; mp: 153°C (Ref. [11] 153°C).

2-(3-Bromophenyl)thiazolo[5,4-c]pyridine (**2g**, $C_{12}H_7BrN_2S$)

Yield: 54%; mp: 118°C; ^{1}H NMR ($CDCl_3$): $\delta = 7.36$ (t, $J = 8.0$ Hz, 1H), 7.62 (d, $J = 8.0$ Hz, 1H), 7.89 (d, $J = 5.9$ Hz, 1H), 7.98 (d, $J = 8.0$ Hz, 1H), 8.26 (s, 1H), 8.61 (d, $J = 5.9$ Hz, 1H), 9.17 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 117.98$ (d), 123.79 (s), 127.05 (d), 131.12 (d), 131.18 (d), 135.01 (s), 135.37 (d), 144.75 (d), 146.51 (d), 146.57 (s), 159.09 (s), 171.86 (s) ppm; EI-MS: m/z (%) = 292 (M^+ (^{81}Br),

32), 290 (M^+ (^{79}Br), 31), 211 (18), 183 (8), 181 (7), 140 (9), 109 (16), 102 (21), 82 (100), 75 (22); CI-MS: m/z (%) = 310 (M^+ (^{81}Br) + NH_4, 3), 308 (M^+ (^{79}Br) + NH_4, 3), 293 (MH^+ (^{81}Br), 97), 291 (MH^+ (^{79}Br), 100), 213 (42), 191 (11); HRCI-MS: $C_{12}H_8{}^{79}BrN_2S$ (MH^+); calcd: 290.9591; found: 290.9592.

Acknowledgements

I thank Professor *K. Smith*, Centre for Clean Chemistry, University of Wales Swansea, UK, for recording the NMR and mass spectra. I also thank the Royal Society of Chemistry for an international author grant.

References

[1] Okafor CO (1972) Int J Sulfur Chem **7B**: 121
[2] Moersdorf P, Schickaneder H, Engler H, Ahrens KH Ger Offen (1987) 3 533 331; (1987) Chem Abstr **107**: 7185a
[3] Shen TY, Clark RL, Pessolano AA, Witzel BE, Lanza TJ Ger Offen (1974) 2 330 109; (1974) Chem Abstr **80**: 95916s
[4] Al-Thebeiti MS (2000) Farmaco **55**: 109
[5] Couture A, Grandclaudon P (1984) Heterocycles **22**: 1383
[6] Couture A, Grandclaudon P, Huguerre E (1987) J Heterocycl Chem **24**: 1765
[7] Katner AS, Brown RF (1990) J Heterocycl Chem **27**: 563
[8] Abdel-Latif FF, Mohammed YS, Abdel-Ghani H, Ahmed Ek, El-Gawish EH (1993) Phosphorus Sulfur Silicon Relat Elem **78**: 251
[9] Al-Ahmadi AA, El-Zohry MF (1994) Phosphorus Sulfur Silicon Relat Elem **97**: 35
[10] Smith K, Anderson D, Matthews I (1995) Sulfur Lett **18**: 79
[11] Smith K, Lindsay CM, Morris IK, Matthews I, Pritchard GJ (1994) Sulfur Lett **17**: 197
[12] See for example: Smith K, El-Hiti GA, Abdo MA, Abdel-Megeed MF (1995) J Chem Soc Perkin Trans **1**: 1029; Smith K, El-Hiti GA, Abdel-Megeed MF, Abdo MA (1996) J Org Chem **61**: 647, 656; El-Hiti GA (1997) Bull Chem Soc Jpn **70**: 2209; Smith K, El-Hiti GA, Abdel-Megeed MF, Abdo MA (1999) Collect Czech Chem Commun **64**: 515
[13] See for example: Abdel-Megeed MF, Aly YL, Saleh MA, Abdo IM, El-Hiti GA, Smith K (1995) Sulfur Lett **19**: 129; Smith K, El-Hiti GA, Hawes AC (1999) Synlett 945; Smith K, El-Hiti GA, Pritchard GJ, Hamilton A (1999) J Chem Soc Perkin Trans **1**: 2299
[14] Giorgi G, Salvini L, Ponticelli F, Tedeschi P (1996) J Heterocycl Chem **33**: 1895; Chimichi S, Tedeschi P, Calvietti S, Ponticelli F (1997) Mag Reson Chem **35**: 601