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Synthesis of substituted thiazolo[4,5-*b*]pyridines and other annulated heterocycles via $S_N2 \rightarrow$ Thorpe–Ziegler $\rightarrow$ Thorpe–Guareschi domino reactions

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ABSTRACT

A new combinatorial method for the preparation of substituted thiazolo[4,5-*b*]pyridines, which utilizes cyanoacetamide, heterocumulenes (isothiocyanates, carbon bisulfide), and ethyl-4-chloroacetoacetate in a new $S_N2 \rightarrow$ Thorpe–Ziegler $\rightarrow$ Thorpe–Guareschi domino reactions has been developed. The obtained thiazolo[4,5-*b*]pyridines were then used together with aldehydes and malononitrile in another Knoevenagel reaction $\rightarrow$ Michael reaction $\rightarrow$ hetero-Thorpe–Ziegler domino reaction for the synthesis of substituted 4,6-dihydro-5*H*-pyrano[2,3-*d*]thiazolo[4,5-*b*]pyridines.

1. Introduction

Substituted thiazolo[2,3-*b*]pyridines represent an important class of annulated heterocycles with diverse types of pharmaceutical[1] and pesticide[2] activity. The practical significance of thiazolo[4,5-*b*]pyridines stimulates the continuous development of synthetic methods for the preparation of these compounds,[3] including combinatorial approaches via solution and solid-phase syntheses.[4]

The majority of known synthetic methods for substituted thiazolo[4,5-*b*]pyridines are two-stage protocols.[2] As such, at the first stage either the thiazole or pyridine cycle is constructed. The second stage of the synthesis is usually the intermolecular cyclocondensation reaction, which forms the second pyridine or thiazole ring. There are also examples of substituted thiazolopyridines obtained from *N*-cyanoiminothiolate salts and polyfunctional haloalkanes, where the primary preparation of 5-substituted 4-aminothiazoles is followed by intramolecular cyclization, which forms the second preannulated pyridine cycle.[4,5] This approach also permits synthesis of 2-*R*-amino(thio)thiazolopyridines from the corresponding salts of *N*-cyanoiminothiolates and 4-bromoacetoacetic ester without the isolation of intermediates.[5] In general approaches that rely on the preliminary synthesis and isolation of *N*-cyanoiminothiolate salts usually restrict the variety of substituents in 2-*R*-amino(thio)thiazolopyridines, result in the formation of by-products, and have a low yield of the final thiazolopyridines.

2. Results and discussion

In this study we describe a new one-pot method of synthesis of substituted 7-hydroxy[1,3]thiazolo[4,5-*b*]pyridine-5(4*H*)-ones using new $S_N2 \rightarrow$ Thorpe–Ziegler $\rightarrow$ Thorpe–Guareschi domino reactions. Several types of domino reactions (see works of Prof. L.F. Tietze[6]) are very well described in literature and are routinely used in the synthesis of various heterocyclic compounds, including some natural products. However, the reactions presented in this study were not previously described and their synthetic potential is not yet known.

We used cyanoacetamide **1**, heterocumulenes (isothiocyanates **2**, carbon bisulfide **3**), and ethyl-4-chloroacetoacetate **4** as starting reagents for our domino reactions. One of the distinctive features of the proposed method is the direct generation of mercaptonitrile salts **5** in the reaction mixture without their preliminary synthesis and isolation (Scheme 1).

We discovered that high yield of the final products can be achieved by introducing the starting reagents to the reaction mixture in a specific sequence and by maintaining a certain temperature regime (Scheme 1). As such, salt **5** was generated in EtOH from equimolar amounts of compounds **1**, **2** or **1**, **3** and KOH at 20 °C. Ethyl-4-chloroacetoacetate **4** was then added to the reaction mixture, followed by an additional equimole of a KOH solution in EtOH. Subsequently, the reaction mixture was refluxed for 30 min to form 2-(*R*-amino)-7-hydroxy[1,3]thiazolo[4,5-*b*]pyridin-5(4*H*)-ones (**9**), which were isolated in 70–82% yields after acidification of the reaction mixture with HCl.

Under these conditions, the formation of compounds **9** proceeds with high regioselectivity, which is a result of the specific sequence of

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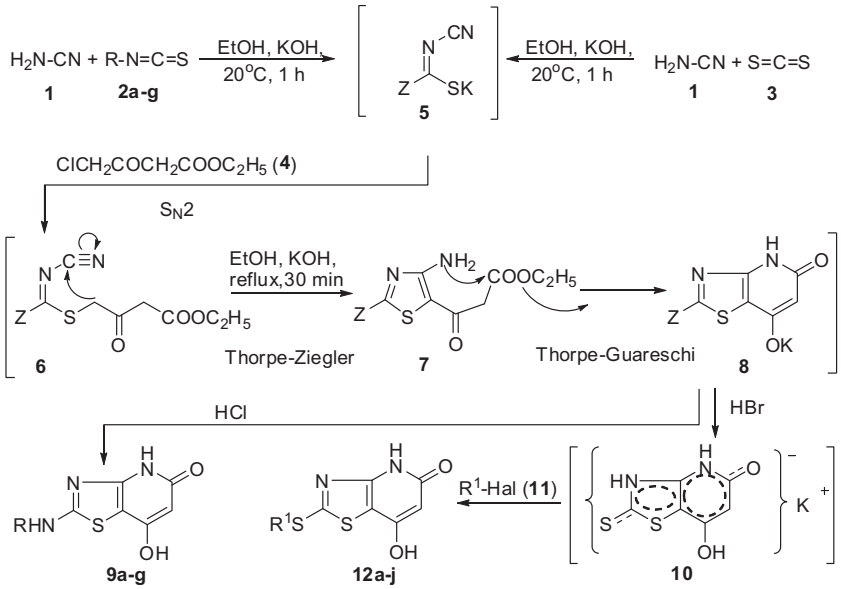


Scheme 1. Synthesis of substituted 7-hydroxy[1,3]thiazolo[4,5-*b*]pyridin-5(4*H*)-ones. Z=NHR, SK. **2**, **9**: R=CH_3 (a); CH_3CH_2 (b); $CH_2CH{=}CH_2$ (c); C_6H_5 (d); 4-OCH_3–C_6H_4 (e); 3-Cl–C_6H_4 (f); 3-F–C_6H_4 (g). **11**, **12**: R^1=CH_3 (a); CH_3CH_2 (b); CH_2–3-C_5H_4N (c); CH_2–2,6-Cl_2–C_6H_3 (d); CH_2–3,4-F_2–C_6H_3 (e); CH_2–3-CF_3–C_6H_4 (f); CH_2–CO–3,4-$(OCH_3)_2$–C_6H_3 (g); CH_2–CONH–Ad^1 (h); CH_2–CONH–3,4-F_2–C_6H_3 (i); CH_2–CONH–2-CF_3–C_6H_4 (j).

domino reactions: S_N2 (intermediate **6**)→Thorpe–Ziegler reaction (intermediate **7**)→Thorpe–Guareschi reaction (intermediate **8**).

A unique combinatorial aspect of the developed protocol is the ability to prepare a solution of thiazolo[4,5-*b*]pyridine-2-thiolate **10** and, without isolating the intermediate, use it in the subsequent S_N2 reaction for the synthesis of pyridin-5(4*H*)-ones **12**. This approach significantly simplifies the preparation of compounds **12** and avoids the isolation and purification of intermediates **5**, **7**.[4,5] Moreover, an almost 2-fold increase in the yield of 2-(*R*-thio)-thiothiazolo[4,5-*b*]pyridinones **12** can probably be attributed to the absence of the 2-alkylthiolate hydrolysis in molecules **12**. Unlike previously described protocols,[4,5] in our method the alkylation reaction was carried out at the end of the synthesis rather than at the beginning.

Salt **5** (Z=SK) was generated in ethanol from cyanoacetamide **1** and carbon bisulfide **3** in the presence of 2 mol of KOH. Salt **5** was then reacted with ester **4** via the S_N2 mechanism to form intermediate **6**. The subsequent intramolecular Thorpe–Ziegler and Thorpe–Guareschi cyclizations proceeded via the formation of intermediate **7** to give di-potassium salt **8** (Z=SK). This transition from salt **5** to salt **8** forms the basis of our domino reaction. Then the reaction mixture was acidified with HCl to obtain a solution of salt **10**, which was divided into equal volumes and equimolar amounts of various *R*-Hal **11** were added to the solutions. The formed precipitates of compounds **12** were isolated by filtration. The high regioselectivity of the final alkylation reaction is probably related to the higher nucleophilicity of the exocyclic sulfur atom compared to the nitrogen or oxygen atoms. A similar behavior of the conjugated thiolato heterocycles in S_N2 reactions has been observed in the past.[7]

The structures of the obtained compounds **9** and **12** were confirmed by NMR and FTIR spectroscopy, and elemental analysis. A characteristic feature of the IR spectra of **9** and **12** is the presence of stretching and bending absorption bands of the C(O)NH and NH groups in the region 1612–1676 cm^{-1} and 2980–3470 cm^{-1}. The absence of characteristic absorption bands of the C≡N, C=O, and NH_2 groups for intermediates **5**–**7** also indicates high regioselectivity of the reaction. The ^1H NMR spectra of compounds **9** and **12** contain, along with the proton signals of R and NH groups, the signals of C^6H, N^4H, and OH protons at 5.14–5.77 ppm and 10.85–11.88 ppm, respectively. In some cases NH protons were not resolved due to deuterium exchange. The multiplicity and position of the proton signals indicate that compounds **9** and **12** exist in a DMSO solution in the same tautomeric form.

In the ^{13}C NMR spectra, the presence of the characteristic signals of the C^2, C^5, C^6, and C^7 atoms at δ 164.2–169.8, 162.9–167.7, 90.7–94.7, and 160.8–165.4 ppm, respectively, also confirms the structures of **9** and **12**.

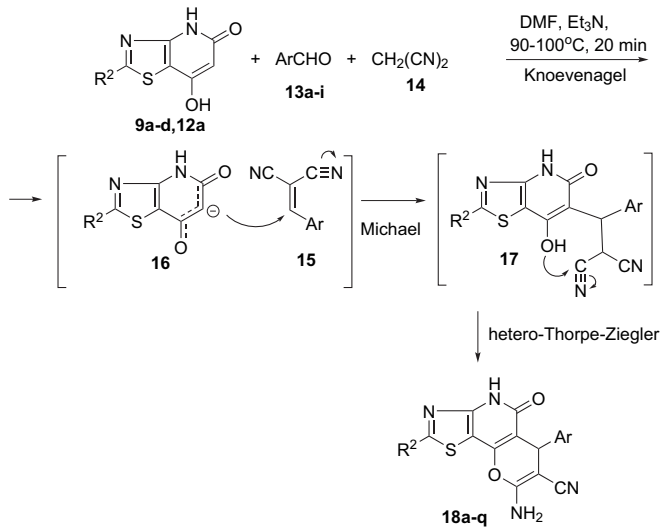
Compounds **9** and **12** represent convenient building blocks for the synthesis of previously unknown substituted 4,6-dihydro-5*H*-pyrano[2,3-*d*][1,3]thiazolo[4,5-*b*]pyridines **18**. The interest in new synthetic pathways toward 2-amino-3-cyano-4*H*-pyranes is related to their anticancer activity.[8] We based a new synthetic method for annulated pyranes on the domino reactions of the following type: Knoevenagel reaction→Michael reaction→hetero-Thorpe–Ziegler reaction.

As such, compounds **18** were synthesized in s single reaction flask by mixing equimolar amounts of starting compounds **9a**–**d** or **12a**, corresponding aldehyde **13**, malononitrile **14**, and Et_3N as a catalyst in DMF (Scheme 2). The reaction was carried out at 90–100 °C for ~20 min.

All added reagents reacted with each other sequentially in a domino process. Most likely, unsaturated nitrile **15** was formed first in the Knoevenagel reaction. Subsequently, anion **16** reacted with nitrile **15** in the Michael reaction to form adduct **17**, which cyclized to pyrane **18** via the Thorpe–Ziegler mechanism. This reaction sequence was partially confirmed by the use of unsaturated nitriles **15** in the synthesis of pyranes, and by the isolation of Michael adducts **17** and their subsequent cyclization into pyrans.[5]

The structures of compounds **18** were confirmed by NMR and FTIR spectroscopy, and elemental analysis. A characteristic feature of the IR spectra of heterocycles **18** is the presence of the high-intensity stretching absorption bands of the C≡N and NH_2 groups at 2188–2204 and 3160–3452 cm^{-1}, respectively. Such absorption bands are characteristic of the IR spectra of compounds containing the conjugated enaminonitrile moiety (H_2N–C=C–CN). The bending absorption band of the NH_2 group overlaps with the absorption bands of the NH and C(O) groups.

The ^1H NMR spectra of compounds **18** show signals of NH_2 and C^6H protons as singlets in the δ 6.95–7.319 and 4.28–4.70 ppm



Scheme 2. Synthesis of substituted 4,6-dihydro-5*H*-pyrano[2,3-*d*][1,3]thiazolo[4,5-*b*]pyridines. **9**: R^2=$NHCH_3$ (a); $NHCH_2CH_3$ (b); $NHCH_2CH{=}CH_2$ (c); NHC_6H_5 (d). **12**: R^2=SCH_3 (a). **13**: Ar=C_6H_5 (a); 4-Cl–C_6H_4 (b); 4-Br–C_6H_4 (c); 4-OCH_3–C_6H_4 (d); 2,3-$(OCH_3)_2$–C_6H_3 (e); 4-$COOCH_3$–C_6H_4 (f); 2-C_4H_3S (g); 3-C_5H_4N (h); 4-C_5H_4N (i). **18**: R^2=$NHCH_3$, Ar=C_6H_5 (a); R^2=$NHCH_3$, Ar=2,3-$(OCH_3)_2$–C_6H_3 (b); R^2=$NHCH_3$, Ar=4-$COOCH_3$–C_6H_4 (c); R^2=$NHCH_3$, Ar=2-C_4H_3S (d); R^2=$NHCH_3$, Ar=4-C_5H_4N (e); R^2=$NHCH_2CH_3$, Ar=4-Cl–C_6H_4 (f); R^2=$NHCH_2CH_3$, Ar=4-OCH_3–C_6H_4 (g); R^2=$NHCH_2CH_3$, Ar=4-$COOCH_3$–C_6H_4 (h); R^2=$NHCH_2CH_3$, Ar=2-C_4H_3S (i); R^2=$NHCH_2CH_3$, Ar=3-C_5H_4N (j); R^2=$NHCH_2CH_3$, Ar=4-C_5H_4N (k); R^2=$NHCH_2CH{=}CH_2$, Ar=4-$COOCH_3$–C_6H_4 (l); R^2=$NHCH_2CH{=}CH_2$, Ar=3-C_5H_4N (m); R^2=NHC_6H_5, Ar=4-Br–C_6H_4 (n); R^2=NHC_6H_5, Ar=4-OCH_3–C_6H_4 (o); R^2=SCH_3, Ar=3-C_5H_4N (p); R^2=SCH_3, Ar=4-C_5H_4N (q).

regions. A characteristic feature of the ^{13}C NMR spectra of compounds **18** is the presence of signals of C^6 and C≡N carbons in the δ 31.7–36.9 and 119.2–120.0 ppm regions. The position of the $C^8{=}C^7$ carbon signals at 158.5–159.3 and 56.7–58.6 ppm indicates the presence of a enaminonitrile moiety ($H_2N–C^8{=}C^7–CN$) in **18** with the p→δ-electron conjugation.

3. Conclusions

In conclusion, we have developed several domino-type protocols: (1) S_N2 reaction→Thorpe–Ziegler reaction→Thorpe–Guareschi reaction and (2) Knovenagel reaction→Michael reaction→hetero-Thorpe–Ziegler reaction, which by themselves or in combinations significantly extend combinatorial potential for the synthesis of new complex heterocyclic systems.

4. Experimental

4.1. 2-(*R*-Amino)-7-hydroxy[1,3]thiazolo[4,5-*b*]pyridin-5(4*H*)-ones 9a–g

Cyanoamide (**1**) (0.42 g, 0.01 mol) was added to a solution of 0.56 g (0.01 mol) of KOH in 20 mL of EtOH with stirring at 20 °C, and 0.01 mol of corresponding isothiocyanate **2** was added after a minute. The reaction mixture was stirred at 20 °C for 1 h; then, 1.37 mL (0.01 mol) of chloroacetoacetic ester (**4**) was added, and a solution of 0.56 g (0.01 mol) of KOH in 20 mL of EtOH was added after 5 min. The reaction mixture darkened, and its temperature increased to ~60 °C. Next, the reaction mixture was refluxed with stirring for 30 min; the mixture was cooled to 20 °C with continuous stirring for 3 h. Then, 15 mL of water was added to the reaction mixture, and the contents were acidified with a 10% solution of HCl to pH 7. The resulting precipitate was filtered off, and successively washed with water (2×15 mL), ethanol (2×10 mL), and hexane (2×15 mL). Compounds **9** were recrystallized from ethanol or nitromethane.

4.2. 7-Hydroxy-2-(*R*-thio)[1,3]thiazolo[4,5-*b*]pyridin-5(4*H*)-ones 12a–j

Cyanoamide (**1**) (2.1 g, 0.05 mol) was added to a solution of 2.8 g (0.05 mol) of KOH in 100 mL of EtOH with stirring at 20 °C. Subsequently, the reaction mixture was quenched with 3.0 mL (0.05 mol) of carbon disulfide (**3**) after 2 min and a solution of 2.8 g (0.05 mol) of KOH in 100 mL of EtOH after another 2 min. The reaction mixture was stirred at 20 °C for 1 h; then, 50 mL of water was added. Next, 6.7 mL (0.05 mol) of chloroacetoacetic ester (**4**) was added dropwise at a temperature of 10–12 °C with intense stirring for 45 min. The resulting solution was diluted with 20 mL of water and filtered through a filter. A solution of 2.8 g (0.05 mol) of KOH in 100 mL of EtOH was added to the filtered reaction mixture. The reaction mixture was refluxed for 30 min with stirring, it was then cooled down to 20 °C, and 5.8 mL (0.05 mol) of hydrobromic acid (density of 1.49 g/mL) was added. The reaction mixture was filtered again through folded filter and a 40% aqueous ethanol solution was added to the resulting solution to obtain 330 mL of the reaction mixture.

The resulting solution of compound **10** was used in 10 different syntheses with 30-mL portions placed in individual flasks. As such, corresponding alkyl halide **11** (0.0045 mol) was added to each portion at 20 °C with stirring, and the reaction mixture was brought to the boiling point. A precipitate was formed. The reaction mixture was kept at 5 °C overnight and the precipitate was filtered off and sequentially washed with water (2×10 mL), ethanol (2×5 mL), and hexane (2×10 mL). Compounds **12** were obtained in 98–100% purity.

4.3. 8-Amino-6-aryl-7-cyano-5-oxo-4,6-dihydro-5*H*-pyrano[2,3-*d*][1,3]thiazolo[4,5-*b*]pyridines 18a–q

A mixture of compounds **9a–d** or **12a** (0.002 mol) was first quenched with aldehydes **13** (0.002 mol) and malononitrile **14** (0.13 g, 0.002 mol) in 15 mL of DMF, and then with triethylamine (0.5 mL). The reaction mixture was heated at 90–100 °C for 20 min and then filtered hot. Filtrate was cooled down and kept in a refrigerator (5 °C) overnight. The formed precipitate was filtered off and washed with hot water (2×10 mL), ethanol (2×5 mL), and hexane (2×15 mL). Compounds **18** were recrystallized from 1,4-dioxane or nitromethane.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.09.045. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. (a) Lin, R.; Johnson, S. G.; Connolly, P. J.; Wetter, S. K.; Binnun, E.; Hughes, T. V.; Murray, W. V.; Pandey, N. B.; Moreno-Mazza, S. J.; Adams, M.; Fuentes-Pesquera, A. R.; Middleton, S. A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2333–2337; (b) Kulkarni, S. S.; Newman, A. H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2987–2991; (c) Komoriya, S.; Kobayashi, S.; Osanai, K.; Yoshino, T.; Nagata, T.; Haginoya, N.; Nakamoto, Y.; Mochizuki, A.; Nagahara, T.; Suzuki, M.; Shimada, T.; Watanabe, K.; Isobe, Y.; Furugoori, T. *Bioorg. Med. Chem.* **2006**, *14*, 1309–1330; (d) Walczynski, K.; Zuiderveld, O. P.; Timmerman, H. *Eur. J. Med. Chem.* **2005**, *40*, 15–23.
2. Litvinov, V. P.; Dozenko, V. V.; Krivokolysko, S. G. The Chemistry of Thienopyridines In. *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Elsevier Academic: Amsterdam, 2007; Vol. 93, pp 117–178.
3. (a) Dolle, R. E.; Le Bourdonnec, B.; Goodman, A. J.; Morales, G. A.; Thomas, C. J.; Zhang, W. *J. Comb. Chem.* **2009**, *11*, 739–790; (b) Dolle, R. E.; Le Bourdonnec, B.; Goodman, A. J.; Morales, G. A.; Thomas, C. J.; Zhang, W. *J. Comb. Chem.* **2008**, *10*,

753–800; (c) Dolle, R. E.; Le Bourdonnec, B.; Goodman, A. J.; Morales, G. A.; Salvino, J. M.; Zhang, W. *J. Comb. Chem.* **2007**, *9*, 855–902; (d) Lee, T.; Lee, D.; Lee, I. Y.; Gong, Y. D. *J. Comb. Chem.* **2010**, *11*, 95–99.
4. (a) Artemov, V. A.; Ivanov, V. L.; Shestopalov, A. M.; Litvinov, V. P. *Tetrahedron* **1997**, *53*, 13351–13360; (b) Ivanov, V. L.; Artemov, V. A.; Shestopalov, A. M.; Nesterov, V. N.; Struchkov, Y. T.; Litvinov, V. P. *Chem. Heterocycl. Compd. (NY)* **1996**, 413–419.
5. Walek, W.; Götzschel, K. *J. Prakt. Chem.* **1979**, *321*, 260–269.
6. Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH : Weinheim, 2006; 617 p.
7. Shestopalov, A. M.; Rodinovskaya, L. A.; Shestopalov, A. A. *J. Comb. Chem.* **2010**, *12*, 9–12.
8. (a) Wood, D. L.; Panda, D.; Wiernicki, T. R.; Wilson, L.; Jordan, M. A.; Sing, J. P. *Mol. Pharmacol.* **1997**, *52*, 437–444; (b) Kasibhatla; Gourdeau, H.; Meerovitch, K.; Drewe, J.; Reddy, L.; Qiu, H.; Zhang, F.; Bergeron, F.; Bbouffard, D.; Yang, Q.; Herich, J.; Lamothe, S.; Cai, S. X.; Tseng, B. *Mol. Cancer Ther.* **2004**, *3*, 1365–1374; (c) Gourdeau, H.; Leblond, L.; Hamelin, B.; Desputeau, C.; Dong, K.; Kianicka, I.; Custeau, D.; Bondreau, C.; Geerts, L.; Cai, S.-X.; Drewe, J.; Labrecque, D.; Kasibhatla, S.; Tseng, B. *Mol. Cancer Ther.* **2004**, *3*, 1375–1385; (d) Litvinov, Y. M. Dissertation. Institute of Organic Chemistry, RAS: Moscow, 2009 [in Russian].