Combinatorial Synthesis of Substituted Thieno[3,2-*b*]pyridines and Other Annulated Heterocycles via New S_N2 → Thorpe−Ziegler → Thorpe−Guareschi Domino Reactions

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Known methods of synthesis of thieno[3,2-*b*]pyridines are significantly underrepresented compared to available information on thieno[2,3-*b*]pyridines.[1,2] Nevertheless, several synthetic pathways toward thieno[3,2-*b*]pyridines have been previously described in the literature.[3−6]

A thieno[3,2-*b*]pyridine structure can be approached via several pathways (Figure 1), all of which require synthesis or in situ generation of 3-aminothiophene. Pathway A was developed by Gronowitz et al.[7] It was successfully used to prepare multiconjugated thieno[3,2-*b*]pyridines via the reaction of ortho-halogenated pyridines with 3-*tert*-butoxycarbonylamino-2-trimethylstannylthiophene.[8] Thieno[3,2-*b*]-pyridines can also be synthesized via pathways B and C using 3-amino-2-carboxy thiophene and β-ethoxymethylene carbonyl compounds (derivatives of ethyl orthoformate and malonodinitrile, acetoacetic ester, cyanoacetic ester, and others).[9−11] For example, the condensation of 3-amino thiophene, triethyl orthoformate, and Meldrum's acid was used to prepare thieno[3,2-*b*]pyridines with anticancer activities.[12] The reaction of 3-amino-2-carboxy thiophene and 4-fluorobenzoyl acetoacetic ester (pathway D) was employed to obtain substituted thieno[3,2-*b*]pyridines, which were used as intermediates in the synthesis of γ-aminobutyric acid receptor modulators.[13] Pathway E was used to synthesize rare pyrrolothienopyridines by the reaction of 3-amidinothiophene with maleic anhydride and the subsequent oxidation of the Diels−Alder adduct.[14]

Thieno[3,2-*b*]pyridines can also be synthesized using an alternative approach by attaching a thiophene ring to pyridine.[15−18] As such, they were prepared via a base catalyzed reaction of 3-halogen-2-cyano(ethoxycarbonyl)-methylene pyridine with heterocumulenes, isothiocyanates, or carbon disulfide.[16−18] Similarly, thieno[3,2-*b*]pyridines annulated with pyridine or pyrimidine were prepared via a one-step method using 3-cyanopyridine-2(1*H*)thiones (or 5-cyanopyridine-6(1*H*)thiones) and 4-chloroacetoacetic ester.[19,20]

Biological properties of thieno[2,3-*b*]pyridines are relatively well studied. Very often, they tend to show higher activities than isomeric thienopyridines.[9,10,13] Substituted thieno[3,2-*b*]pyridines are also known for their biologically properties. Among them were found potential ligands for the

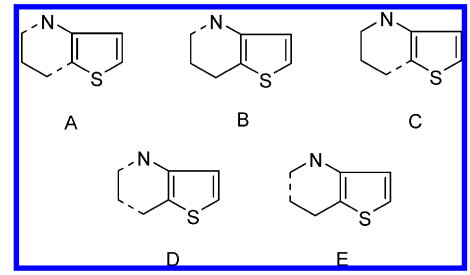


Figure 1. Possible approaches toward thieno[3,2-*b*]pyridines.

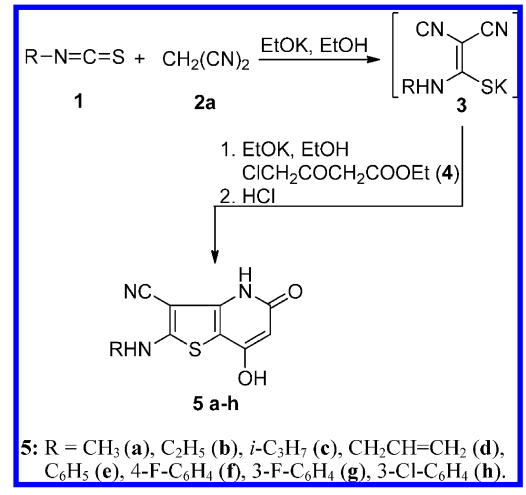
γ-aminobutyric acid receptor,[13] immunomodulators,[2,4,13] Ca channel inhibitors,[13,21] and herbicides.[13]

Considering the practical importance of thieno[3,2-*b*]pyridines and a limited number of methods available for their synthesis, we decided to developed a new regioselective protocol for preparation of these compounds based on a domino-type reaction. The reaction includes the following consecutive steps: the S_N2 reaction → the Thorpe−Ziegler reaction → the Thorpe−Guareschi reaction, and significantly differs from the well-known domino pathways previously described by Tietze.[22]

Thieno[3,2-*b*]pyridines were prepared by generating potassium salts of 2-amino-2,2-dicyanoethylene-2-thiolate **3** from isothiocyanates **1** and malonodinitrile (**2**) and reacting **3** with 4-chloroacetoacetic ester **4**. We determined that the reaction proceeds at elevated temperatures in the presence of potassium ethoxide and gives thieno[3,2-*b*]pyridines **5a**−**h** in high yields (75−93%) after acidification of the reaction mixture to pH ∼ 7 (Scheme 1).

The IR spectra of compounds **5** contain a characteristic absorption band of the conjugated cyano-group in the 2204−2216 cm^{-1} region. The NMR spectra of **5** show corresponding R, NH, and OH signals, and includes a singlet peak that corresponds to the C^6H hydrogen atom in the δ.5.15−6.06 ppm region. The IR spectra of **5** also demonstrate an intense CONH absorption band in the 1612−1644 cm^{-1} region, which suggests that **5** also exist in a pyridine-5(4*H*)-one tautomeric form, similar to pyridine-2(1*H*)-ones [1].

Scheme 1



5: R = CH_3 (**a**), C_2H_5 (**b**), *i*-C_3H_7 (**c**), $CH_2CH{=}CH_2$ (**d**), C_6H_5 (**e**), 4-F-C_6H_4 (**f**), 3-F-C_6H_4 (**g**), 3-Cl-C_6H_4 (**h**).

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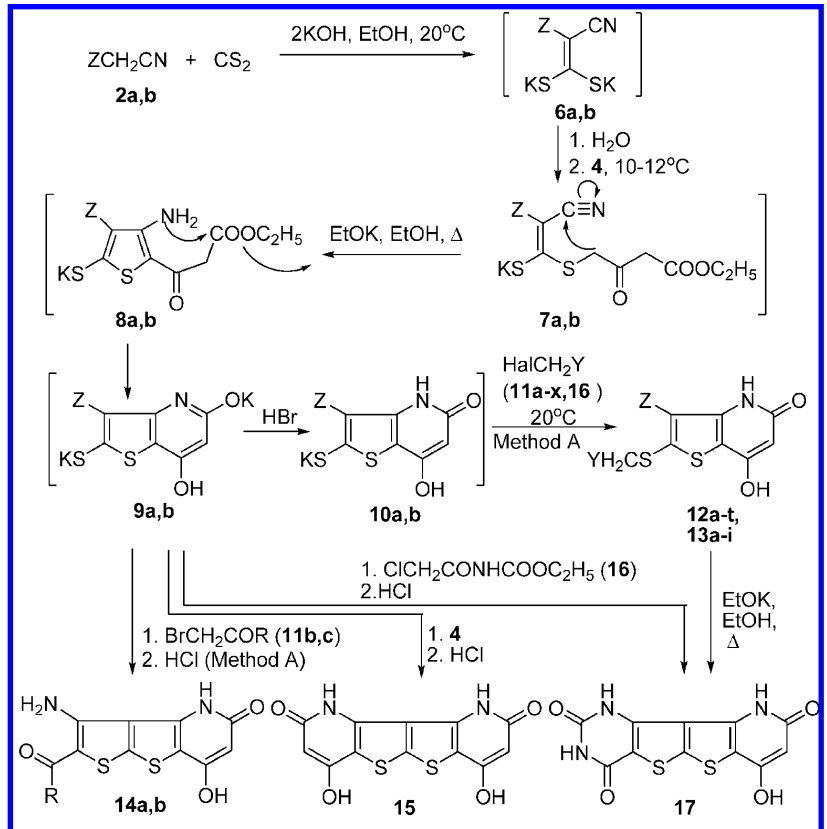
Scheme 2



2, 6-10: Z = CN (**a**), $CONH_2$ (**b**).
12: Z = CN, **13:** Z = $CONH_2$.
14: R = CO-Ad^1 (**a**), CO-Ph (**b**).

	Hal	Y		Y
11a	I	H	**12a**	H
11b	Br	Ad^1-CO-	**12b**	Ad^1-CO
11c	Br	Ph-CO-	**12c**	Ph-CO
11d	Cl	3-F-C_6H_4-	**12d**	3-F-C_6H_4
11e	Br	4-Br-C_6H_4-	**12e**	4-Br-C_6H_4
11f	Cl	4-Cl-C_6H_4-	**12f**	4-Cl-C_6H_4
11g	Cl	4-CH_3-C_6H_4-	**12g**	4-CH_3-C_6H_4
11h	Cl	3-CH_3-C_6H_4-	**12h**	3-CH_3-C_6H_4
11i	Cl	3-CF_3-C_6H_4-	**12i**	3-CF_3-C_6H_4
11j	Cl	3- CH_3O -C_6H_4-	**12j**	3-CH_3O-C_6H_4
11k	Cl	4-C_5H_4N-	**12k**	4-C_5H_4N
11l	Cl		**12l**	
11m	Cl	-CO-NH-$CH(CH_3)_2$	**12m**	CO-NH-$CH(CH_3)_2$
11n	Cl	CO-NH-C_3H_5	**12n**	CO-NH-C_3H_5
11o	Cl	Ad^1-NH-CO-	**12o**	Ad^1-NH-CO
11p	Cl	3-F-C_6H_4-NH-CO-	**12p**	3-F-C_6H_4-NH-CO
11q	Cl	3-F_3C-C_6H_4-NH-CO-	**12q**	3-F_3C-C_6H_4-NH-CO
11r	Cl	4-F_3C-C_6H_4-NH-CO-	**12r**	4-F_3C-C_6H_4-NH-CO
11s	Cl	3,4-F_2-C_6H_3-NH-CO-	**12s**	3,4-F_2-C_6H_3-NH-CO
16	Cl	$CONHCOOC_2H_5$	**12t**	$CONHCOOC_2H_5$
11a	I	H	**13a**	H
11t	Cl	Ph-	**13b**	Ph
11g	Cl	4-CH_3-C_6H_4-	**13c**	4-CH_3-C_6H_4
11h	Cl	3-CH_3-C_6H_4-	**13d**	3-CH_3-C_6H_4
11u	Cl	2-CH_3-C_6H_4-	**13e**	2-CH_3-C_6H_4
11v	Cl	2,4-Cl_2-C_6H_3-	**13f**	2,4-Cl_2-C_6H_3
11w	Cl	Ph-CH_2	**13g**	Ph-CH_2
11x	Br	$COOCH_3$	**13h**	$COOCH_3$
11b	Br	Ad^1-CO-	**13i**	Ad^1-CO

The combinatorial potential of the described method is determined by the number of available isothiocyanates and derivatives of cyanoacetic acid (malonodinitrile, cyanothioacetamides). The potential of this reaction can be doubled by substituting isothiocyanates with other heterocumulenes, such as carbon disulfide. Moreover, the total possible outcome of this method can be further expanded in geometric progression by adding additional steps to the reaction

sequence. Such a strategy opens new preparation pathways not only toward substituted thieno[3,2-*b*]pyridines, but also toward more complex multiconjugated heterocyclic systems (Scheme 2).

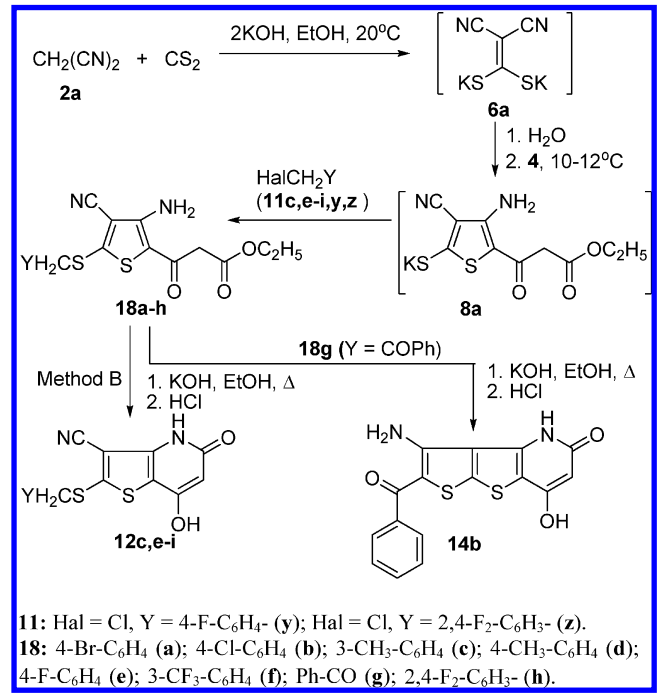
Dipotassium 2,2,-dicyano-1,1-dithiolate (**6a**) or dipotassium 2-cyano-2-carbamoyl-1,1-dithiolate (**6b**) were generated in the ethanol solution by the reaction of malonodinitrile or cyanothioacetamide (**2b**) with carbon disulfide in the presence of two equivalents of KOH (Scheme 2). Subsequently, the reaction mixture was diluted with water (25% of total volume) and slowly reacted with 1 equiv of 4-chloroacetoacetic ester under vigorous stirring at 10−12 °C. Under such conditions, the S_N2 reaction proceeds highly regioselectively and gives intermediate **7** as the only product. Consequently, KOH in the solution catalyzes the Thorpe−Ziegler and Thorpe−Guareschi reactions and forms pyridine ring **9**.

To obtain compounds **12** and **13**, the reaction mixture was neutralized with 1 equiv of 48% HBr, filtered to remove an inorganic salt, and diluted with ethanol. Subsequently, the solution was divided into equal portions (up to 50 aliquots), and each portion was reacted at room temperature with alkyl halides **11a**−**x**, **16** (method A). Intermediate **9** has several nucleophilic centers, nonetheless, the reaction proceeds highly regioselectively at the sulfur atom and forms thieno[3,2-*b*]pyridine-5-ones **12**, **13** in 38−93% yields. Similar selectivity was observed in the past for 2-amino-5-cyanopyrimidine-6-thiolates,[23] 3-cyano-6-hydroxypyrimidine-2-thiolates,[24] substituted 1,4-dihydropyridine-2-thiolates,[20,25] and 1,2,3,4-tetrahydro-2-oxopyridine-6-thiolates.[26] Thieno[3′,2′:4,5]thieno[3,2-*b*]pyridin-5(4*H*)-ones **14a**,**b** were obtained without initial acidification of the reaction mixture. As such, the solution of **9** was reacted with α-halogen ketones **11b**,**c** at 60−70 °C for 10 min and subsequently neutralized with an excess of HCl. The formation of compounds **14** proceeds via successive S_N2 and the Thorpe−Ziegler reactions, analogous to many other examples of the reactions between cyanopyridine thiones and α-halogen ketones.[1] New heterocyclic systems **15** and **17** were obtained by reacting dipotassium salt **9a** with 4-chloroacetoacetic ester **4** or chloroacetyl urethane **16**. Both of these reactions proceed via the usual S_N2 → Thorpe−Ziegler → Thorpe−Guareschi pathway, which was supported by obtaining **17** upon refluxing thieno[3,2-*b*]pyridine-5-one **12t** in ethanol.

The structures of compounds **12**, **13**, **14**, **15**, and **17** were confirmed by IR, NMR, and MS analyses (see the Supporting Information). The IR spectra of **12** and **13** contain N^4HC^5═O and $CONH_2$ absorption bands in the 1584−1664 and 1640−1664 cm^{-1} regions. The ^1H NMR spectra show a broaden N^4H signal at ∼11.9 ppm, which is characteristic of all pyridine-2(1*H*)-thiones [1]. A ^{13}C NMR signal of the N^4HC^5═O fragment appears at 160−164 ppm, which supports the presence of the pyrimidone ring in **12** and **13**.

By modifying the conditions, we confirmed to a certain extent the sequence of reactions leading to compounds **12**. As such, when salt **6** was heated for several minutes with 4-chloroacetoacetic ester without the excess of KOH, the reaction stopped at thienylacetoacetic ester **8a**. Subsequently, the reaction mixture was divided into several portions, which were reacted with

Scheme 3



11: Hal = Cl, Y = 4-F-C_6H_4- (**y**); Hal = Cl, Y = 2,4-F_2-C_6H_3- (**z**).
18: 4-Br-C_6H_4 (**a**); 4-Cl-C_6H_4 (**b**); 3-CH_3-C_6H_4 (**c**); 4-CH_3-C_6H_4 (**d**); 4-F-C_6H_4 (**e**); 3-CF_3-C_6H_4 (**f**); Ph-CO (**g**); 2,4-F_2-C_6H_3- (**h**).

corresponding alkyl halogenides **11** to give compounds **18** in good to high yields (73−92%, Scheme 3).

The structures of molecules **18** were supported by IR, ^1H NMR, ^{13}C NMR, MS, and elemental analyses. The IR spectra of **18** contain valent and deformation absorption bands of the NH_2-group at 1604−1632 and 3164−3428 cm^{-1}, and absorption bands of the COOR− and conjugated CN-groups at 1712−1740 and 2212−2218 cm^{-1}. Probably, the C═O group forms intramolecular hydrogen bond with the neighboring NH_2-group (Figure 2), which leads to the shift of the C═O absorption band into the low region and its partial overlap with the NH_2 deformation band.

The ^1H NMR spectra of compounds **18** contain characteristic signals of Et, NH_2, and Y-groups, and $CH_2(CO)$ singlet signals at the 3.47−3.68 ppm. The ^{13}C NMR spectra show C═O signals at 151.62−155.25 ppm. This also supports the hydrogen bond formation instead of the possible enolization of the acetoacetic ester fragment.

Compounds **18a**−**d**,**f**,**g** were converted into **12c**,**e**−**i** in 62−75% yields via the Thorpe−Guareschi reaction under refluxing in ethanol at the presence of a base (method B). When compound **18g** (Y = COPh) was refluxed with an excess of a base, it gave triannulated heterocycle **14b** in a 70% yield.

Compound **5** has several reaction centers and, therefore, can be further modified. Previously, we have demonstrated that 4-hydroxypyridine-2(1*H*)-ones can be utilized in synthesis of annulated 2-amino-4*H*-pyrans,[20] some of which have demonstrated an anticancer activity.[27] Here, we utilized compounds **5** in a similar reaction to prepare annulated

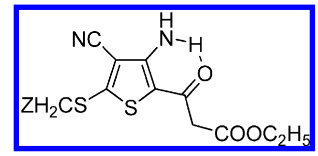
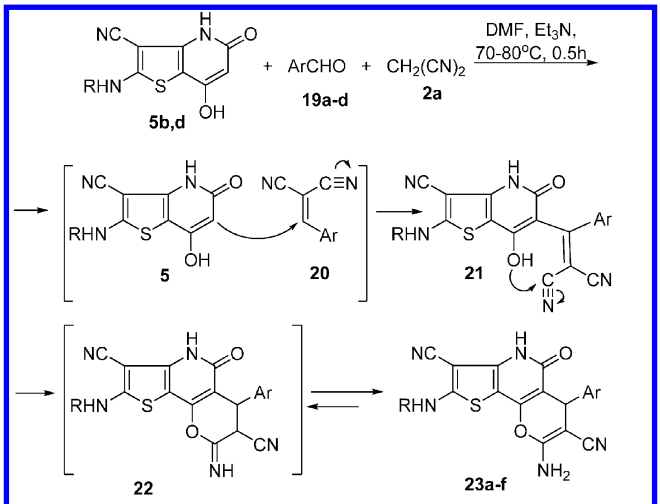


Figure 2. Intramolecular H-bond in ethyl 3-{3-amino-5-[*R*-methylenthio]-4-cyanothien-2-yl}-3-oxopropanoates.

Scheme 4



19: Ar = 4-Cl-C_6H_4 (**a**); 3-C_5H_4N (**b**); 4-C_5H_4N (**c**); 2-OCH_3-C_6H_4 (**d**).
23: R = C_2H_5, Ar = 4-Cl-C_6H_4 (**a**); R = C_2H_5, Ar = 3-C_5H_4N (**b**); R = C_2H_5, Ar = 4-C_5H_4N (**c**); R = $CH_2CH{=}CH_2$, Ar = 2-OCH_3-C_6H_4 (**d**); R = $CH_2CH{=}CH_2$, Ar = 3-C_5H_4N (**e**); R = $CH_2CH{=}CH_2$, Ar = 4-C_5H_4N (**f**).

pyrans. As such, a three-component condensation of **5b**,**d** with aldehydes **19** and malononitrile (**2a**) in DMF at 70−80 °C in the presence of Et_3N gives pyrans **23a**−**f** with high regioselectivity and 74−89% yields (Scheme 4).

Most likely, this domino-type reaction proceeds via the Knoevenagel → the Michael → and the Thorpe−Ziegler steps. This is supported by the numerous examples of stepwise pyrans syntheses, where unsaturated nitriles are first prepared via the Knoevenagel reaction and then used in the Michael reaction with 1,3-dicarbonyl compounds.[20,27] Subsequently, the resulting Michael adducts undergo cyclization and 1,3-sigmatropic shift and form 2-amino-4*H*-pyrans **23**. The ^1H NMR spectra of **23** contain NH_2 and C^6H singlets in the 7.17−7.20 and 4.43−4.48 ppm regions. Similar to **5**, **12**, **14**, **15**, and **17**, compounds **23** exist in a tautomeric form of pyridine-5(1*H*)-ones. The ^{13}C NMR spectra of **23** contain characteristic C(O)NH signals at 158.25−158.77 ppm.

In conclusion, we have developed several domino-type protocols: (1) S_N2 reaction → Thorpe−Ziegler reaction → Thorpe−Guareschi reaction, (2) double domino reaction S_N2 reaction → Thorpe−Ziegler reaction → Thorpe−Guareschi reaction, (3) S_N2 reaction → Thorpe−Ziegler reaction, and (4) Knoevenagel reaction → Michael reaction → hetero-Thorpe−Ziegler reaction, which by themselves or in combinations significantly extend combinatorial potential for the synthesis of new complex heterocycle systems.

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Supporting Information Available. Detailed experimental procedures and compound characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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