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New regio-selective method of combinatorial synthesis of substituted thiophenes, thieno[3,2-*b*]pyridines and other heterocycles via combination of 'domino'-type reactions

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ABSTRACT

We present a novel combinatorial multicomponent regio-selective approach towards the synthesis of thieno[3,2-*b*]pyridines and pyridine pyrans. The methodology is based on the 'domino'-type reaction. The high regio-selectivity in this reaction is gained by the in situ generation of the mono-potassium salt of 2-cyano-1-mercaptoethenethiolate. We also demonstrate that the use of ethyl 2-cyanoacetate in this reaction as a CH-acid leads to the termination of the domino sequence at the Dieckmann condensation step and yields novel ethyl 3-(4-cyano-3-hydroxy-5-(alkylthio)thiophen-2-yl)-3-oxopropanoate.

1. Introduction

Substituted thieno[3,2-*b*]pyridines are pharmacologically important molecules with several types of biological activity. Previously, they were demonstrated as γ-aminobutyric acid ligands,[1] immune modulators,[1,2] inhibitors of calcium channels,[1] and as herbicides.[1] Thiophenes, containing N-substituted amides in the three positions, have become an interest of several recent studies.[3] These molecules and their derivatives annulated with carbo- and heterocycles were shown as cannabinoid receptor ligands,[4] tumor growth inhibitors,[5] AMPA receptor modulators,[6] dihydroorthotetragenase inhibitors,[7] herbicides,[8] and mammalian hyperproliferative disorders agents.[9]

Previously, we explored the synthesis of thieno[3,2-*b*]pyridines using thiophene derivatives as primary scaffolds.[10] In another study, the thieno[3,2-*b*]pyridine structure was constructed from a pyridine derivative.[1] We also demonstrated a one-pot synthesis of thieno[3,2-*b*]pyridines directly from cyanodithioethylene salts with concomitant cyclization of both thiophene and pyridine rings. Using this methodology, we synthesized 7-hydroxy-5-oxo-2-(*R*-methylenthio)-4,5-dihydrothieno[3,2-*b*]pyridines from dipotassium 2-cyanoethene-1,1-ditiolathe and 4-chloroacetoacetic ester.[10] Similarly, a dipotassium *N*-cyanodithioimidocarbonate and 4-chloroacetoacetate were used in the domino reaction to prepare 7-hydroxy[1,3]thiazolo[4,5-*b*]pyridin-5(4*H*)-ones.[11] However, the yield of the synthesized compounds was moderate to low. It is known that the dipotassium or disodium salts reacts with 1 equiv of α-halogenated carbonyl compounds and give mixtures of S-mono- and *S*,*S*-disubstituted unsaturated nitriles.[12] Moreover, for reaction mixtures of chloro-acetonitrile and disodium 2,2-dicyanoethylene-1,1-bis(thiolate) at any molar ratios the reaction always proceeds as two S_N2 and two Thorpe–Ziegler condensations and yields thienothiophenes.[12] This creates significant complications for the facile combinatorial synthesis of heterocyclic libraries.

2. Results and discussion

Here, we demonstrate a novel combinatorial, multicomponent, and highly regio-selective method for the preparation of thieno[3,2-*b*]pyridines **9** with combination of CH-acids **1** (Fig. 1) and alkylhalides **8** (Fig. 2). The proposed methodology is unique and is based on the initial in situ generation of the mono-potassium salt of 2-cyano-1-mercaptoethenethiolates **3** directly from CH-acids **1a**–**f**, carbon disulfide **2** and 1 equiv of potassium hydroxide.

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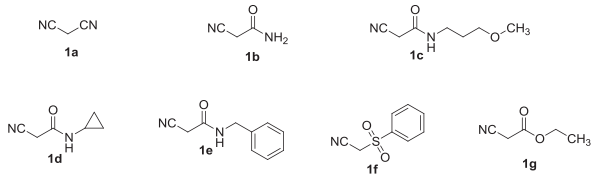


Fig. 1. CH-acids **1a**–**g**.

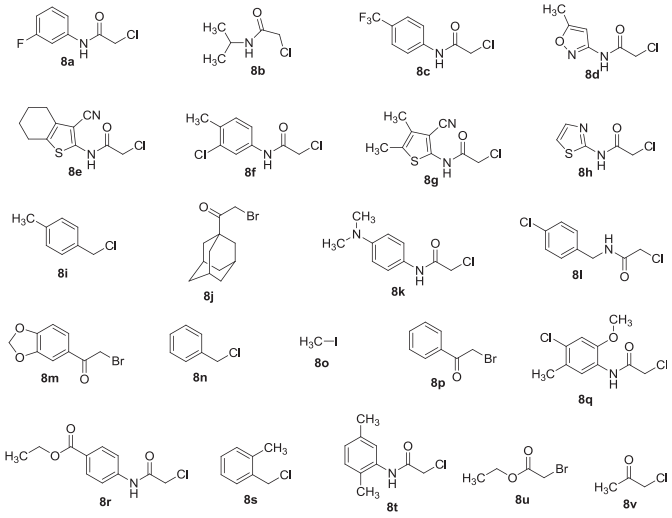
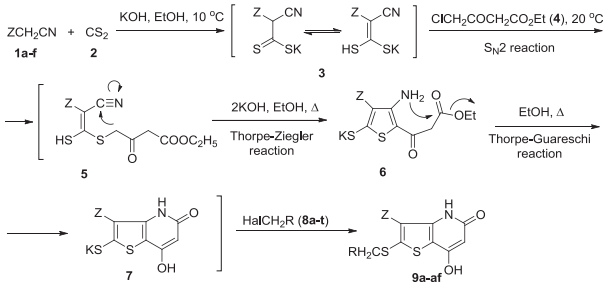


Fig. 2. Alkylhalides **8a**–**v**.

The following S_N2 reaction of salts **3** and 4-chloroacetoacetic ester **4** proceeds with high regio-selectivity at only one sulfur atom in contrast to the dipotassium salt reaction, which consumes both sulfur atoms.[12,13]

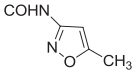
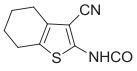
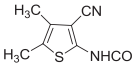
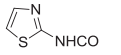
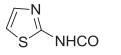
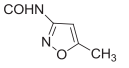
The subsequent 'domino'-type Thorpe–Ziegler and Thorpe–Guareschi reactions begin after the addition of two more equivalents of potassium hydroxide and conclude with the formation of potassium salt of thieno[3,2-*b*]pyridine **7** (Scheme 1). The solution of salt **7** is then divided into portions and reacted with alkylhalides **8a**–**t**. The remarkable regio-selectivity of each step ensures the high yields (58–88%) of final substituted thieno[3,2-*b*] pyridines **9a**–**af** in this five-step multicomponent one-pot synthesis (Table 1).



Scheme 1. Synthesis of thieno[3,2-*b*]pyridines **9a**–**af**.

Here for the first time, beside malonodinitrile (**1a**) and cyanoacetamide (**1b**), we used *N*-substituted cyanoacetamides: N-(3-methoxypropyl)- (**1c**), *N*-cyclopropyl- (**1d**), *N*-benzylcyanoacetamide (**1e**), and phenylsulfonyl acetonitrile (**1f**). These new CH-acids significantly expand the variety of synthetically available thieno [3,2-*b*]pyridines and provides access to molecules with pharmacologically important functional groups (Tables 2 and 3).

Table 1
Thieno[3,2-*b*]pyridines **9a**–**af**

Entry	Product	Z	R	Yield, %
1	**9a**	CN	3-F–C_6H_4–NHCO	59 (43[10])
2	**9b**	CN	$(CH_3)_2$CH–NHCO	62 (46[10])
3	**9c**	CN	4-CF_3–C_6H_4–NHCO	58 (38[10])
4	**9d**	CN		65
5	**9e**	CN		73
6	**9f**	CN	3-Cl–4-CH_3–C_6H_3–NHCO	58
7	**9g**	CN		82
8	**9h**	CN		64
9	**9i**	$CONH_2$	4-CH_3–C_6H_4	88 (86[10])
10	**9j**	$CONH_2$	Ad[1]–CO	87 (86[10])
11	**9k**	$CONH_2$	4-$(CH_3)_2$N–C_6H_4–NHCO	70
12	**9l**	$CONH_2$	4-Cl–C_6H_4–CH_2NHCO	63
13	**9m**	$CONH_2$	$(CH_3)_2$CHNHCO	58
14	**9n**	$CONH_2$	3,4-OCH_2O–C_6H_3–CO	59
15	**9o**	$CONH_2$		60
16	**9p**	$CONH_2$		59
17	**9q**	$CH_3O(CH_2)_3NHCO$	C_6H_5	75
18	**9r**	$CH_3O(CH_2)_3NHCO$	H	72
19	**9s**	$CH_3O(CH_2)_3NHCO$	C_6H_5CO	83
20	**9t**	$CH_3O(CH_2)_3NHCO$	2-OCH_3–4-Cl–5-CH_3–C_6H_2–NHCO	61
21	**9u**	$CH_3O(CH_2)_3NHCO$	4-C_2H_5OOC–C_6H_4–NHCO	59
22	**9v**		2-CH_3–C_6H_4	75
23	**9w**		4-CH_3–C_6H_4	84
24	**9x**		2-OCH_3–4-Cl–5-CH_3–C_6H_2–NHCO	58
25	**9y**		C_6H_5CO	85
26	**9z**		H	86
27	**9aa**	$C_6H_5CH_2NHCO$	4-CH_3–C_6H_4	84
28	**9ab**	$C_6H_5CH_2NHCO$	H	76
29	**9ac**	C_6H_5 SO_2	4-CH_3–C_6H_4	70
30	**9ad**	$C_6H_5SO_2$	C_6H_5	63
31	**9ae**	$C_6H_5SO_2$	C_6H_5CO	66
32	**9af**	$C_6H_5SO_2$	2,5-$(CH_3)_2$–C_6H_3–NHCO	60

The structures of the prepared compounds were confirmed using NMR and IR analyses. The IR spectra of compounds **9a**–**af** contain characteristic absorption bands of the amide group and pyridine ring at 3360–3240 cm^{-1} and the absorption band of the carbonyl group at 1630 cm^{-1}. The IR spectra of phenylsulfonyl derivatives **9ac**–**af** contain signals of the SO_2R group at 1170 and 1130 cm^{-1}. ^1H NMR spectra of compounds **9a**–**af** show NH- and OH- proton peaks and a characteristic C(6)H peak at 5.77–6.08 ppm.

The reaction of cyanoacetic ester **1g** with carbon sulfide and α-halogengeminal compounds containing electron-withdrawing moieties lead to the formation of 4-amino-3-ethoxycarbonyl