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Syntheses of Functionalized Thieno[3,4-*d*]imidazoles and Thieno[3,2-*d*]pyrimidines from Chlorine-Containing Enamidonitriles

S. V. Popil'nichenko, S. G. Pil'o, V. S. Brovarets, and B. S. Drach

Institute of Bioorganic and Petroleum Chemistry, National Academy of Sciences of Ukraine, ul. Murmanskaya 1, Kiev, 02660 Ukraine;
e-mail: drach@bpci.kiev.ua

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Abstract — Enamidonitriles of the general formula Cl(X)C=C(CN)NHCOR readily react with methyl sulfanylacetate to give tri- or tetra-substituted thiophenes, which can be converted into new functional derivatives of thieno[3,2-*d*]pyrimidine and thieno[3,4-*d*]imidazole.
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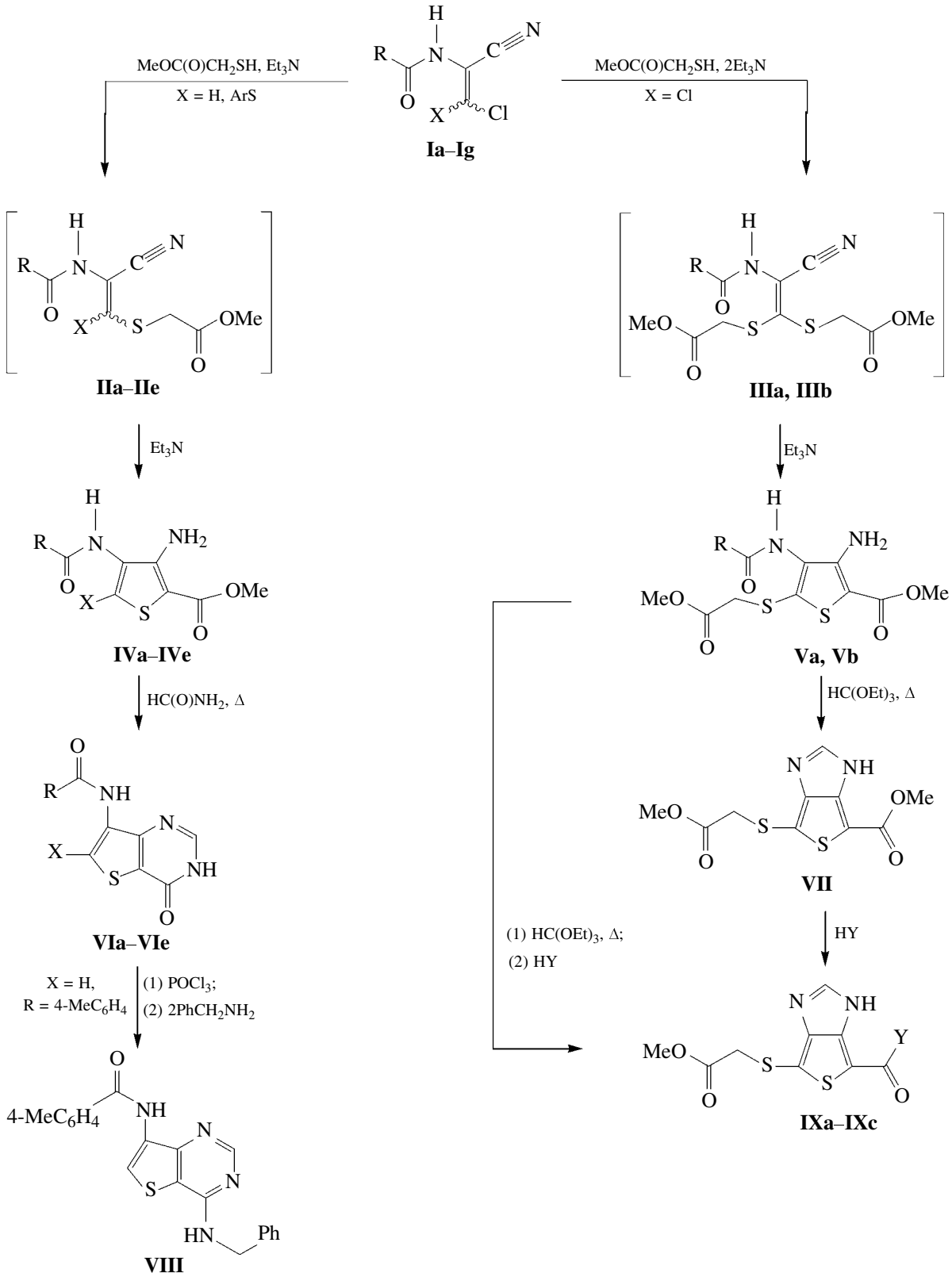
Accessible chlorine-containing enamidonitriles **I** were previously used for the preparation of a series of nonfused azole derivatives; these syntheses were reviewed in [1] and also considered in recent publications [2–4]. In the present work we studied a new way of using compounds **I** in the synthesis of functionally substituted thiophenes and their fused ring derivatives. As shown in Scheme 1, enamidonitriles **I** having one or two labile chlorine atoms reacted with methyl sulfanylacetate in the presence of triethylamine to give initially intermediates **II** and **III** which then underwent intramolecular ring closure involving the triple C≡N bond and active methylene group. As a result, the corresponding functionally substituted thiophenes **IV** and **V** were obtained (Table 1). Analogous base-catalyzed cyclizations of various compounds posses-

Table 1. Yields, melting points, and elemental analyses of compounds **IV**–**IX**

Comp. no.	Yield, %	mp, °C (solvent for crystallization)	Found, %		Formula	Calculated, %	
			N	S		N	S
IVa	64	164–166 (EtOH)	10.22	11.45	$C_{13}H_{12}N_2O_3S$	10.14	11.60
IVb	66	157–159 (EtOH)	9.59	11.10	$C_{14}H_{14}N_2O_3S$	9.65	11.04
IVc	58	138–140 (EtOH)	6.95	16.15	$C_{20}H_{18}N_2O_3S_2$	7.03	16.09
IVd	70	186–188 (EtOH)	6.61	15.28	$C_{19}H_{15}N_2O_3S_2Cl$	6.69	15.31
IVe	53	168–171 (EtOH)	6.49	14.83	$C_{20}H_{17}N_2S_2O_3Cl$	6.47	14.81
Va	71	130–133 (EtOH)	7.15	16.74	$C_{16}H_{16}N_2O_5S_2$	7.36	16.86
Vb	65	150–151 (EtOH)	7.01	16.23	$C_{17}H_{18}N_2O_5S_2$	7.10	16.26
VIa	62	>300 (AcOH)	15.44	11.83	$C_{13}H_9N_3O_2S$	15.49	11.82
VIb	59	286–288 (AcOH)	14.69	11.21	$C_{14}H_{11}N_3O_2S$	14.73	11.24
VIc	68	275–277 (AcOH)	10.60	16.35	$C_{20}H_{15}N_3O_2S_2$	10.68	16.30
VId	63	240–242 (AcOH)	10.09	15.41	$C_{19}H_{12}N_3O_2S_2Cl$	10.15	15.49
VIe	61	235–237 (AcOH)	9.79	14.93	$C_{20}H_{14}N_3O_2S_2Cl$	9.82	14.98
VII	68	193–195 (EtOH)	9.81	22.45	$C_{10}H_{10}N_2S_2O_4$	9.78	22.40
VIII	65	182–184 (EtOH)	14.91	8.62	$C_{21}H_{18}N_4OS$	14.96	8.56
IXa	52	228–230 (AcOH)	10.34	23.67	$C_9H_8N_2O_4S_2$	10.29	23.55
IXb	59[a]	233–235 (EtOH)	10.72	16.31	$C_{16}H_{14}N_3O_3S_2Cl$	10.61	16.20
IXc	61	237–239 (EtOH)	10.29	15.78	$C_{18}H_{19}N_3O_4S_2$	10.36	15.81

[a] Method *a*.

Scheme 1.



R = Ph (**Ia, Ic, Id, If, IIa, IIc, IId, IIIa, IVa, IVc, IVd, Va, VIa, VIc, VId**), 4-MeC_6H_4 (**Ib, Ie, Ig, IIb, IIe, IIIb, IVb, IVe, Vb, VIb, VIe**); X = H (**a, b**), 4-MeC_6H_4S (**c**), 4-ClC_6H_4S (**d, e**), Cl (**f, g**); **IX**: Y = HO (**a**), 4-$ClC_6H_4CH_2NH$ (**b**), 4-$MeOC_6H_4CH_2CH_2NH$ (**c**).

Table 2. IR and ^{1}H NMR spectral parameters of compounds **IV**–**IX**

Comp. no.	IR spectrum, ν, cm^{-1} (KBr)	^{1}H NMR spectrum, δ, ppm (DMSO-d_6)
IVa	1625 (δ_{NH_2}), 1645 (NC=O), 1690 (OC=O), 3050–3250 (NH as.), 3370, 3450 (NH_2)	3.76 s (3H, OCH_3), 6.55 br.s (2H, NH_2), 7.52 m ($3H_{arom}$), 7.85 s (1H, C^5H), 7.93 m ($2H_{arom}$), 9.81 s (1H, NH)
IVb	1610 (δ_{NH_2}), 1645 (NC=O), 1690 (OC=O), 3350, 3440 (NH, NH_2)	2.41 s (3H, CH_3), 3.76 s (3H, OCH_3), 6.53 br.s (2H, NH_2), 7.30 d ($2H_{arom}$), 7.82 s (1H, C^5H), 7.83 d ($2H_{arom}$), 9.70 s (1H, NH)
IVc	1645[a] (NC=O, δ_{NH_2}), 1685 (OC=O), 3170, 3225 (NH, NH_2)	2.31 s (2H, CH_3), 3.69 s (3H, OCH_3), 6.36 br.s (2H, NH_2), 7.22 d ($2H_{arom}$), 7.37 d ($2H_{arom}$), 7.53 m ($3H_{arom}$), 8.00 d ($2H_{arom}$), 9.83 s (1H, NH)
IVd	1605 (δ_{NH_2}), 1650 (NC=O), 1675 (OC=O), 3250, 3380, 3490 (NH, NH_2)	3.72 s (3H, OCH_3), 6.33 br.s (2H, NH_2), 7.37 s ($4H_{arom}$), 7.53 m ($3H_{arom}$), 7.97 d ($2H_{arom}$), 9.81 s (1H, NH)
IVe	1620 (δ_{NH_2}), 1640 (NC=O), 1690 (OC=O), 3180–3250 (NH as.), 3340, 3430 (NH_2)	2.40 s (3H, CH_3), 3.72 s (3H, OCH_3), 6.30 br.s (2H, NH_2), 7.27 d ($2H_{arom}$), 7.37 s ($4H_{arom}$), 7.86 d ($2H_{arom}$), 9.74 s (1H, NH)
Va	1640 (NC=O), 1675 (OC=O), 1745 (OC=O), 3250, 3400 (NH, NH_2)	3.66 s (3H, OCH_3), 3.75 s (5H, CH_2, OCH_3), 6.28 br.s (2H, NH_2), 7.50 m ($3H_{arom}$), 8.02 d ($2H_{arom}$), 9.75 s (1H, NH)
Vb	1640 (NC=O), 1675 (OC=O), 1745 (OC=O), 3200, 3450 (NH, NH_2)	2.41 s (3H, CH_3), 3.66 s (3H, OCH_3), 3.72 s (2H, CH_2), 3.76 s (3H, OCH_3), 6.19 br.s (2H, NH_2), 7.30 d ($2H_{arom}$), 7.91 d ($2H_{arom}$), 9.64 s (1H, NH)
VIa[b]	1670[a] (C=O), 2800–3500 (NH as.)	7.55 m ($3H_{arom}$), 7.99 d ($2H_{arom}$), 8.20 s, 8.35 s (2H, C^6H, C^2H), 9.80 s (1H, NH), 12.53 br.s (1H, NH)
VIc	1675[a] (C=O), 2800–3400 (NH as.)	2.34 s (3H, CH_3), 7.21 d ($2H_{arom}$), 7.40 d ($2H_{arom}$), 7.53 m ($3H_{arom}$), 8.02 d ($2H_{arom}$), 8.08 d (1H, C^2H, $^3J_{HH}$ 2.4 Hz), 10.19 s (1H, NH), 12.52 br.s (1H, NH)
VId	1685[a] (C=O), 2800–3450 (NH as.)	7.43 m ($7H_{arom}$), 8.00 d ($2H_{arom}$), 8.12 d (1H, C^2H, $^3J_{HH}$ 2.8 Hz), 10.24 s (1H, NH), 12.58 br.s (1H, NH)
VId	1680[a] (C=O), 2750–3180 (NH as.)	2.41 s (1H, CH_3), 7.30 d ($2H_{arom}$), 7.41 d.d ($4H_{arom}$), 7.91 d ($2H_{arom}$), 8.12 d (1H, C^2H, $^3J_{HH}$ 3.0 Hz), 10.18 s (1H, NH), 12.61 br.s (1H, NH)
VIIc	1700 (OC=O), 1740 (OC=O), 3050–3130 (NH as.)	3.63 s (3H, OCH_3), 3.83 s (2H, CH_2), 3.94 s (3H, OCH_3), 8.25 s (1H, C^4H), 12.51 br.s (1H, NH)
VIII	1660 (C=O), 3250–3400 (NH as.)	2.42 s (3H, CH_3), 4.77 d (2H, CH_2, $^3J_{HH}$ 6.0 Hz), 7.35 m ($7H_{arom}$), 7.89 d ($2H_{arom}$), 8.27 s, 8.46 s (2H, C^6H, C_2H), 8.50 t (1H, NH), 9.60 s (1H, NH)
IX[a]	1695[a] (C=O), 2400–3200 (NH as., OH as.)	3.86 s (3H, OCH_3), 3.88 s (2H, CH_2), 9.00 s (1H, C^4H), 9.24 br.s (2H, NH, OH)
IXb	1650 (NC=O), 1695 (OC=O), 3050–3140 (NH as.)	3.83 s (3H, OCH_3), 3.89 s (2H, CH_2), 4.24 d (2H, CH_2), 7.17 d ($2H_{arom}$), 7.32 d ($2H_{arom}$), 8.65 s (1H, C^4H), 8.67 t (1H, NH), 12.63 br.s (1H, NH)
IXc	1645 (NC=O), 1690 (OC=O), 3070–3160 (NH as.)	2.61 t (2H, CH_2), 3.20 s (3H, OCH_3), 3.24 m (2H, CH_2), 3.71 s (3H, OCH_3), 3.82 s (2H, CH_2), 6.75 d ($2H_{arom}$), 7.03 d ($2H_{arom}$), 8.13 t (1H, NH), 8.21 s (1H, C^4H), 12.49 br.s (1H, NH)

[a] A band with a shoulder. [b] Mass spectrum: *m/z* 271 (M^+). [c] Mass spectrum: *m/z* 286 (M^+).

sing an O=C–CH_2–S–C=C–C–N fragment have been studied in sufficient detail [5, 6]. The disappearance of C≡N bond and active methylene group and formation of a primary amino group in the transformations **II**–**IV** and **III**–**V** were confirmed by the IR and ^{1}H NMR data (Table 2). The structure of new thiophene-2-carboxylic acid derivatives **IV** and **V** is consistent with spectral data; it was also proved by their transformations into fused heterocycles **VI** and **VII**, respectively (Scheme 1). The transformation **IV**–**VI** occurring by the action of formamide indicates that the methoxycarbonyl and amino groups in the initial compound are located at the neighboring carbon atoms of the thiophene ring. Numerous examples of analogous pyrimidine ring fusion were reported previously [7–9]. Examples of fusion of an imidazole

ring to thiophene via reaction with ethyl orthoformate are also known [10], though they are fewer in number. Elimination of the acyl residue during the transformation **V**–**VII** was confirmed by the mass spectral data (Table 2).

Finally, it should be noted that the transformations **VI**–**VIII** and **VII**–**IX** can be regarded as particular cases of modification of functional substituents in the thieno[3,2-*d*]pyrimidine and thieno[3,4-*d*]imidazole systems. These reactions attract interest not only from the viewpoint of confirming the structure of compounds **VI** and **VII** but also as synthetic routes to fused heterocyclic systems which are difficult or impossible to obtain by other methods; this aspect will be considered in detail in our further publications.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Specord M-80 spectrometer. The 1H NMR spectra were measured from solutions in DMSO-d_6 relative to TMS (internal) on a Varian VXR-300 instrument. The mass spectra were obtained on a Varian MAT-311A spectrometer.

Methyl 4-acylamino-3-aminothiophene-2-carboxylates IVa and IVb *(general procedure).* Methyl sulfanylacetate, 0.011 mol, and triethylamine, 0.01 mol, were added to a solution of 0.01 mol of compound **Ia** or **Ib** in 30 ml of anhydrous acetonitrile, the mixture was heated for 8 h at 60°C, the solvent was removed under reduced pressure, the residue was treated with water, and the precipitate was filtered off and purified by recrystallization.

Methyl 4-acylamino-3-amino-5-arylsulfanylthiophene-2-carboxylates IVc–IVe were synthesized in a similar way from nitriles **Ic**–**Ie**.

Methyl 4-acylamino-3-amino-5-(methoxycarbonylmethylsulfanyl)thiophene-2-carboxylates Va and Vb *(general procedure).* Methyl sulfanylacetate, 0.0082 mol, and triethylamine, 0.0082 mol, were added to a solution of 0.004 mol of nitrile **If** or **Ig** in 30 ml of anhydrous acetonitrile. The mixture was heated for 10 h under reflux, the solvent was removed under reduced pressure, and the residue was treated with water. The product was filtered off and purified by recrystallization from ethanol.

7-Acylamino-3,4-dihydrothieno[3,2-*d*]pyrimidin-4-ones VIa and VIb *(general procedure).* A mixture of 0.01 mol of compound **IVa** or **IVb** and 10 ml of formamide was heated for 7 h at the boiling point. The mixture was then treated with water, and the precipitate was filtered off and recrystallized from acetic acid.

7-Acylamino-6-arylsulfanyl-3,4-dihydrothieno-[3,2-*d*]pyrimidin-4-ones VIc–VIe were synthesized in a similar way from substituted thiophenes **IVc**–**IVe**.

Methyl 4-methoxycarbonylmethylsulfanyl-1*H*-thieno[3,4-*d*]imidazole-6-carboxylate (VII). A mixture of 0.002 mol of compound **Va** or **Vb**, 8 ml of triethyl orthoformate, and 1–2 drops of acetic anhydride was heated for 6 h at the boiling point. The mixture was cooled, and the precipitate was filtered off and purified by recrystallization.

***N*-(4-Benzylaminothieno[3,2-*d*]pyrimidin-7-yl) 4-methylbenzenecarboxamide (VIII).** A mixture of 0.01 mol of compound **VIb**, 5 ml of phosphoryl chloride, and 0.01 mol of *N,N*-dimethylaniline was heated for 5 h under reflux. Volatile substances were removed under reduced pressure, the residue was treated with water, the precipitate was filtered off, dried, and dissolved in 30 ml of acetonitrile, 0.022 mol of benzylamine was added to the solution, the mixture was heated for 10 h under reflux, the solvent was removed under reduced pressure, the residue was treated with water, and the precipitate was filtered off and purified by recrystallization.

4-Methoxycarbonylmethylsulfanyl-1*H*-thieno-[3,4-*d*]imidazole-6-carboxylic acid (IXa). A solution of 0.004 mol of compound **VII** in 10 ml of sulfuric acid was heated for 1 min at 110°C. It was then cooled and poured onto ice, and the precipitate was filtered off and purified by recrystallization.

Methyl 6-(*p*-chlorobenzylcarbamoyl)-1*H*-thieno[3,4-*d*]imidazole-4-ylsulfanylacetate (IXb). *a*. A mixture of 0.004 mol of compound **Va**, 8 ml of triethyl orthoformate, and 0.3 ml of acetic anhydride was heated for 2 h under reflux, 0.006 mol of *p*-chlorobenzylamine was added, and the mixture was heated for an additional 2 h under reflux. The precipitate was filtered off and purified by recrystallization.

b. A solution of 0.004 mol of compound **VII** and 0.008 mol of *p*-chlorobenzylamine in 10 ml of dimethylformamide was heated for 3 h at 110°C. The mixture was cooled, 20 ml of water was added, and the precipitate was filtered off and recrystallized from ethanol. Yield 72%; no depression of the melting point was observed on mixing samples of **IXb** prepared according to methods *a* and *b*; their IR and ^{1}H NMR spectra were also identical.

Methyl 6-[2-(*p*-methoxyphenyl)ethylcarbamoyl)-1*H*-thieno[3,4-*d*]imidazole-4-ylsulfanylacetate (IXc) was synthesized as described above for compound **IXb** (method *a*) from substituted thiophene **Va** and 2-(*p*-methoxyphenyl)ethanamine.

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