Synthesis of Thieno[2,3-*d*]imidazoles by Copper-Catalyzed Amidine Cyclization

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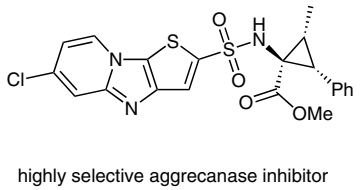
Abstract: A new synthetic approach to thieno[2,3-*d*]imidazoles is presented on the basis of the *N*′-(3-halothiophen-2-yl)amidine cyclization under copper-catalyzed cross-coupling. Using commercially available starting materials such as 2-aminothiophenes or their Boc-protected derivatives and copper catalysts, this method offers a convenient route to a wide range of thieno[2,3-*d*]imidazole derivatives, especially the 5-alkyl-subtituted thieno[2,3-*d*]imidazoles.

Key words: amidines, cyclization, copper, thiophenes, imidazoles

The imidazole unit is a common structural motif in biologically active molecules (Figure 1), being derived from the amino acid histidine.[1] Its ring-fused analogues are well known in clinical therapy under brand names such as Sildenafil, Udenafil and Granisteron.[2] Preclinical studies of thieno[2,3-d]imidazole derivatives have shown activity in the treatment of osteoarthritis,[3] hepatitis C[4] and gastric acid regulation.[5]

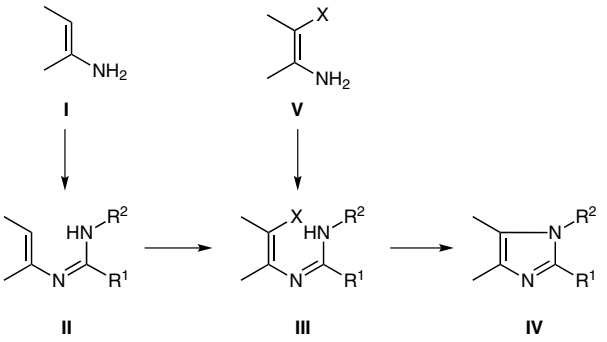


highly selective aggrecanase inhibitor

Figure 1 Biologically active thieno[2,3-*d*]imidazoles

The range of synthetic approaches to thieno[2,3-*d*]imidazoles is limited, especially for derivatives with 1,2-disubstitution on the imidazole core. Construction of the fused imidazole moiety on the thiophene ring may start from 2-nitro-3-aminothiophene derivatives. These can be converted into substituted 2,3-diamines by standard reactions. Subsequent treatment of the products with PPA,[6] triethoxymethane[7] or bromocyane[8] leads to the formation of thieno[2,3-*d*]imidazoles. Condensation of 5-bromo-1*H*-imidazole-4-carbaldehyde derivatives with thioglycolic acid amide[9] or methyl ester[10] is the probably the most general synthetic approach to thieno[2,3-*d*]imidazoles. There is also an Ullmann-type protocol by which thieno[2,3-*d*]imidazoles can be obtained by reaction of 2-bromothiophen-3-isocyanides with primary amines.[11] However, none of these approaches affords 5-alkyl-substituted thieno[2,3-*d*]imidazoles. Furthermore, each procedure includes several steps with resultant low overall yields.

A synthesis of imidazoles including N-arylation and heteroarylation under copper catalyst has been developed in recent years.[12] Using complexes of Cu(I/II) formed in situ or under ligand-free conditions, the imidazole moiety could be obtained from amidines by cyclization of 2-halogen-1-amidine **III** into imidazole **IV** (Scheme 1),[13] C–H functionalization/C–N bond formation[14] or via diamination of terminal alkynes.[15] Derivates **III** could be obtained from the appropriate amines **I** and **V** and imidoyl chlorides, amides or thioamides. Herein we report an approach to thieno[2,3-*d*]imidazoles based on the cyclization of thiophene amidines **III** using copper(I) as catalyst.



Scheme 1 General approach to the ring-fused imidazoles by copper-catalyzed amidines cyclization

Commercially available ethyl 5-amino-3-methylthiophene-2-carboxylate (**1**) was used as starting material (Scheme 2). Reaction of **1** with imidoyl chlorides at room temperature led to amidines **2a**,**b** in 60–69% yield. Further reaction of **2a**,**b** with NBS gave the corresponding bromides **3a**,**b** in 74–79% yield. Previously we have developed a synthetic protocol for cyclization of *N*-halopyrazolylamidines into imidazo[4,5-*c*]pyrazoles.[16] Here we designed reaction conditions for the thiophene derivatives with model compound **2a**. We examined the influence of solvent, ligand, and base on the course of the copper-catalyzed intramolecular arylation (Table 1). The nature of the solvent proved to be the most significant pa-

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rameter controlling the reaction efficiency as was found for the *N*-halopyrazolylamidines derivatives.[16] In all cases, using DMSO or DMF led to an increase in yield of the target product. Another important factor was the appropriate choice of ligand, as seen from entries 9, 10, 15–18 in Table 1, DMEDA and L-Pro appeared most advantageous among the compounds conventionally used in such syntheses (cf. with 1,10-phenanthroline and 8-hydroxyquinoline). Although using cesium carbonate as a base afforded the highest conversion, potassium carbonate gave only a slightly reduced yield. Potassium phosphate turned out to be inefficient (cf. entries 9, 10 vs. 11). Therefore, the inexpensive and effective potassium carbonate was selected as the preferred base for the cyclization. The synthesis of **4b** was carried out under similar conditions in 93% yield.

To explore the scope and limitations of our approach we examined a range of thiophene derivatives. 2-Amino-5-methylthiophene (**7**) was selected as starting material as the simplest example (Scheme 3). This was obtained from 5-methylthiophene-2-carboxylic acid (**5**) using a Curtius rearrangement protocol.[17] However, although **7** formed *N*-(5-methylthiophen-2-yl)acetamide with acetic anhydride[17] it was unreactive toward *N*-methylbenzimidoyl chloride in the presence of Et_3N; only decomposition products of **7** were observed by LCMS analysis in the reaction mixture after 24 hours of stirring in 1,4-dioxane at room temperature.

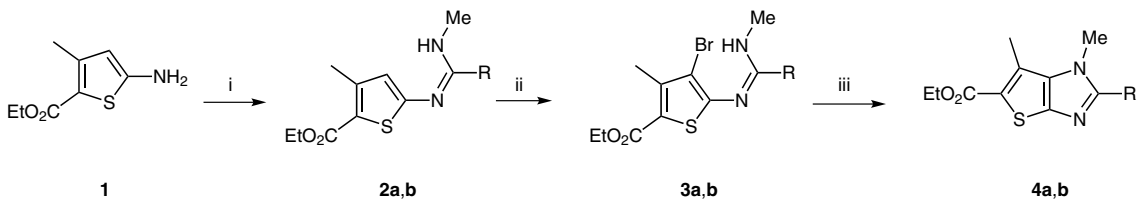
We then decided to examine the Boc-protected precursor **6** to avoid the instability of the aminothiophene derivatives (Scheme 3). Reaction of **6** with sodium hydride in THF followed by addition of *N*-methylbenzimidoyl chloride led to amidine **9** in 72% yield. We examined several halogenation protocols (such as bromine–iodine in methanol, bromine in AcOH with or without sodium acetate, NBS/NIS with or without $KHCO_3$). However all of them resulted in complex mixtures and did not lead to **11**. To circumvent this, we first halogenated **6** with bromine in methanol to form **10** in 74% yield.[18] Reaction of **10** with sodium hydride in THF with *N*-methylbenzimidoyl chloride led to carbamate **11** in 62% yield. The Boc-protecting group was then removed by HCl in 1,4-dioxane, and compound **12** was obtained. After six hours of refluxing of the thieno[2,3-*d*]imidazole with copper(I) catalyst the final product **13** was obtained in 92% yield as the pure product.

Table 1 Condition Optimization for the Cyclization of **3a** into **4a**[a]

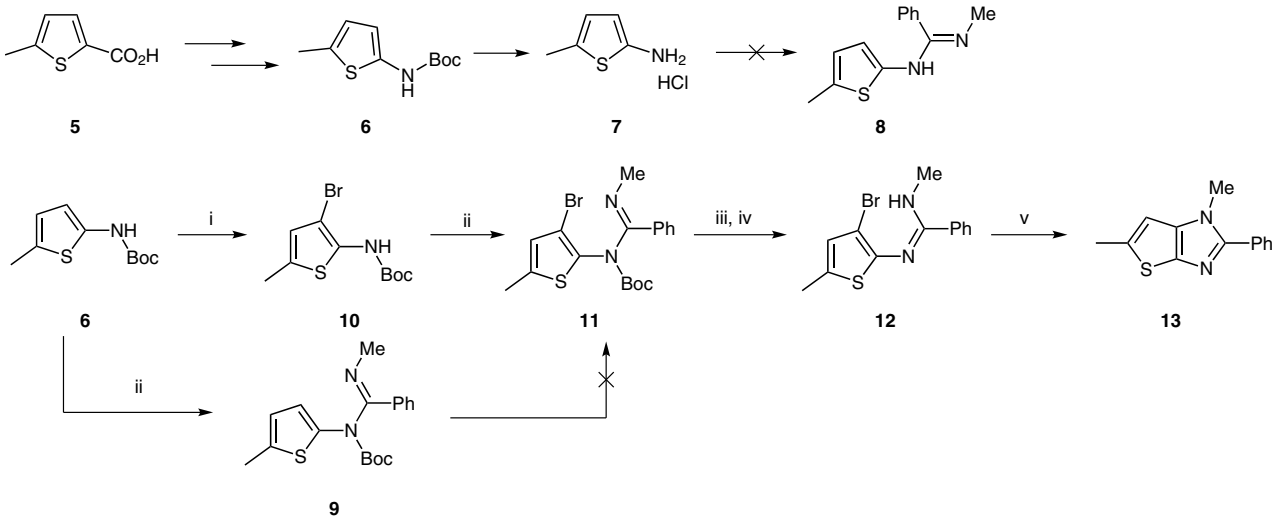
Entry	Solvent	Ligand[b]	Base	Conv. (%)
1	toluene	DMEDA	K_2CO_3	0
2	toluene	DMEDA	Cs_2CO_3	7
3	toluene	8-Oxy	K_2CO_3	3
4	toluene	8-Oxy	Cs_2CO_3	0
5	toluene	Phen	K_2CO_3	21
6	toluene	Phen	Cs_2CO_3	18
7	MeCN	DMEDA	K_2CO_3	6
8	MeCN	Phen	K_2CO_3	12
9	DMF	DMEDA	K_2CO_3	87
10	DMF	DMEDA	Cs_2CO_3	91
11	DMF	DMEDA	K_3PO_4	56
13	DMF	8-Oxy	K_2CO_3	8
14	DMF	Phen	K_2CO_3	34
15	DMF	no ligand	K_2CO_3	0
16	DMF	no ligand and CuI	K_2CO_3	0
17	DMSO	L-Pro	K_2CO_3	76
18	DMSO	L-Pro	Cs_2CO_3	81

[a] Conditions: amidine (1 mol), base (2 mol), CuI (0.05 mol), ligand (0.1 mol), solvent (5 mL), stirring for 6 h, and heating at reflux. The conversion value is given as the average of three independent experiments.
[b] DMEDA = *N*,*N*′-dimethylethylenediamine; Phen = 1,10-phenanthroline; 8-Oxy = 8-hydroxyquinoline.

In conclusion, a new synthetic route to thieno[2,3-*d*]imidazole derivatives based on the cyclization of *N*′-(3-halothiophen-2-yl)amidines under copper-catalyzed cross-coupling conditions has been developed.[19] The facile and inexpensive method using 2-aminothiophenes or their Boc-protected derivatives and copper catalysts allows a variety of substituents to be introduced at all positions of the thieno[2,3-*d*]imidazole scaffold. This approach affords a novel access to different 5-alkyl-subtituted thieno-[2,3-*d*]imidazoles.



Scheme 2 *Reagents and conditions*: (i) 1,4-dioxane, Et_3N, RC(Cl)NMe; (ii) MeCN, NBS; (iii) DMF, CuI, DMEDA, K_2CO_3; **a**: R = Ph; **b**: R = 3-ClC_6H_4.



Scheme 3 *Reagents and conditions*: (i) MeOH, Br_2, $KHCO_3$; (ii) 1,4-dioxane, NaH, PhC(Cl)NMe; (iii) 1,4-dioxane, HCl; (iv) NaOH, MeOH; (v) CuI (5% mol), DMEDA (10% mol), K_2CO_3 (2.0 mol), DMF, reflux.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(19) **General Procedure for Amidines Cyclization**: A round-bottom flask was charged with *N*′-halothiophenylamidine (0.84 mmol), K_2CO_3 (1.68 mmol), DMEDA (0.084 mmol) and anhyd DMF (3 mL). To the stirred mixture was then added powdered CuI (0.042 mmol) under Ar. The stirred mixture was heated under Ar and monitored by TLC, evaporated, diluted with CH_2Cl_2 (100 mL), and filtered. The organic layer was washed with H_2O (2 × 50 mL), dried over Na_2SO_4, filtered and concentrated to give the pure product. **Ethyl 1,6-Dimethyl-2-phenyl-1*H*-thieno[2,3-*d*]imidazole-5-carboxylate (4a)**: yield: 91%; mp 118–120 °C; R_f 0.38 (25% EtOAc–hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.37 (t, *J* = 9.0 Hz, 3 H, Et), 2.82 (s, 3 H, Me), 3.95 (s, 3 H, Me), 4.33 (q, *J* = 9.0 Hz, 2 H, Et), 7.45–7.55 (m, 3 H, 3 × CH), 7.55–7.75 (m, 2 H, 2 × CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.4, 147.2, 137.8, 129.8, 129.3, 129.2, 128.8, 123.3, 60.7, 33.4, 14.3, 13.0. Anal. Calcd for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33. Found: C, 64.03; H, 5.15; N, 9.22. **Ethyl 2-(3-Chlorophenyl)-1,6-dimethyl-1*H*-thieno[2,3-*d*]imidazole-5-carboxylate (4b)**: yield: 93%; mp 167–168 °C; R_f 0.40 (25% EtOAc–hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.38 (t, *J* = 7.1 Hz, 3 H, Et), 2.82 (s, 3 H, Me), 3.97 (s, 3 H, Me), 4.33 (q, *J* = 7.1 Hz, 2 H, Et), 7.40–7.49 (m, 2 H, 2 × CH), 7.49–7.60 (m, 1 H, CH), 7.63–7.71 (m, 1 H, CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.3, 14.4, 30.5, 60.4, 123.9, 127.3, 129.0, 129.4, 129.8, 130.0, 131.5, 134.6, 137.8, 147.1, 154.3, 163.8. Anal. Calcd for $C_{16}H_{15}ClN_2O_2S$: C, 57.40; H, 4.52; N, 8.37. Found: C, 57.02; H, 4.75; N, 8.50. **1,5-Dimethyl-2-phenyl-1*H*-thieno[2,3-*d*]imidazole (13)**: yield: 92%; mp 110–115 °C; R_f 0.20 (25% EtOAc–hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.56 (s, 3 H, Me), 3.82 (s, 3 H, NMe), 6.62 (s, 1 H, CH), 7.34–7.45 (m, 1 H, CH), 7.48 (t, *J* = 7.8 Hz, 2 H, 2 × CH), 7.67 (d, *J* = 7.1 Hz, 2 H, 2 × CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.0, 33.7, 106.8, 128.6, 128.7, 130.7, 137.9, 138.2, 141.8, 150.7. Anal. Calcd for $C_{13}H_{12}N_2S$: C, 68.38; H, 5.30; N, 12.27. Found: C, 68.12; H, 5.50; N, 12.45.

