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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7199–7203

A concise and optimized four-step approach toward 2-(aryl-)alkylsulfanyl-, 4(5)-aryl-, 5(4)-heteroaryl-substituted imidazoles using alkyl- or arylalkyl thiocyanates

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Received 19 June 2006; revised 26 July 2006; accepted 28 July 2006
Available online 17 August 2006

Abstract—A convenient cyclization method leading to trisubstituted imidazoles in up to 84% yield is reported. Diverse 1-aryl-, 2-heteroaryl-substituted ethanones are converted into the corresponding α-oximino derivatives which are reduced under regioselective conditions. The obtained α-amino carbonyl intermediates are reacted with alkyl- or arylalkyl thiocyanates to directly yield C^2–S-substituted imidazoles.

1. Introduction

Pyridinyl imidazoles are the preferred synthetic scaffolds for compounds targeting protein kinases, for example, p38 mitogen-activated protein (MAP) kinase.[1,2] These kinases are involved in signal transduction pathways for pro-inflammatory cytokines. Potential indications include the pathogenesis of chronic inflammatory diseases like rheumatoid arthritis,[3] osteoarthritis, or Crohn's disease accompanied with nonphysiologically increased cytokine levels. The major pro-inflammatory cytokines, interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α), can trigger autoimmune processes that may destroy bone, cartilage, and tissue through mechanisms beyond upholding chronic inflammation. An augmented release of pro-inflammatory cytokines can be promoted by the activation of MAP kinases,[4] for example, the p38 family, in response to stimuli like infection or cellular stress (osmotic shock, UV irradiation). MAP kinases can modify the phosphorylation status of transcription factors implicated in cell proliferation and differentiation processes. An advancement in the therapy of chronic inflammatory diseases is believed to occur by normalizing cytokine levels to physiological values by orally available drugs. In both in vitro and in animal model studies, p38α MAP kinase activity was significantly inhibited in a competitive manner by synthetic compounds derived from the first generation pyridin-4-yl imidazole SB 203580 (**1**) (Fig. 1); these inhibitors were effective at nM–μM concentrations.[5,6] Since Lee and co-workers[7] identified the serine/threonine protein kinase involved in the regulation of inflammatory cytokine biosynthesis as the target for 2,4-diaryl-5-pyridin-4-yl-imidazoles,[8] the structural requirements for p38α MAP kinase inhibition have been extensively discussed. Thus, MAP kinases have recently become an attractive research objective for 'small molecules' that interrupt the inflammatory cascade at a very early point. 2-Thioimidazoles are reported to have some advantages over the prototype SB-like 2-arylimidazoles, for example, fewer interactions with metabolic enzymes like CYP-450.[9] To provide a simple and rapid access to a diversity of 2-(aryl-)alkylsulfanyl-, 4(5)-aryl-, 5(4)-heteroaryl-substituted imidazoles, we developed an optimized and easily handled general thioimidazole synthesis based on the Marckwald's[10] process. Indeed, several current references describe formation of imidazoles from KSCN, but only a few methods have been described that function through regio-controlled production of *N*-substituted imidazoles by the use of substituted isothiocyanates. However, so far, no practical evidence exists for the one-step production of

Keywords: Trisubstituted imidazoles; Alkyl-/arylalkyl thiocyanates; p38 MAP kinase inhibitors.
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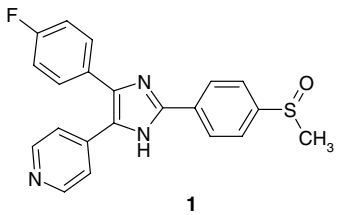
doi:10.1016/j.tetlet.2006.07.147



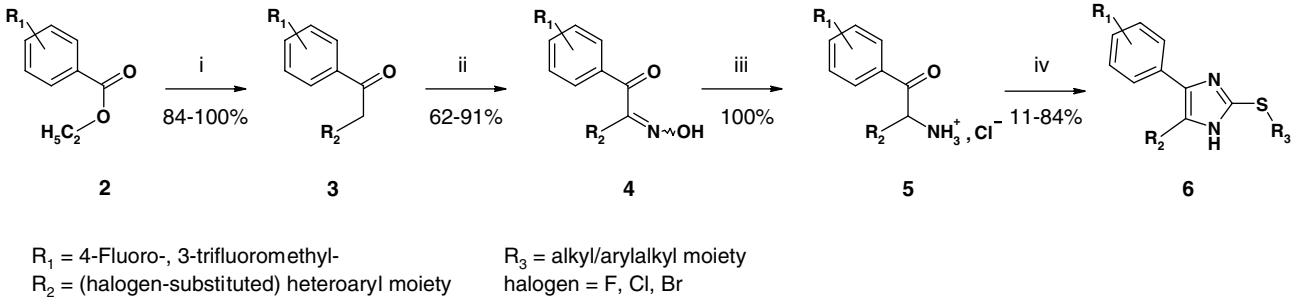
1

Figure 1. First generation prototype inhibitor SB203580 (**1**).

C^2–S-substituted imidazoles **6** from diverse 1-aryl-2-heteroaryl-substituted α-amino ethanones using alkyl- or arylalkyl thiocyanates.

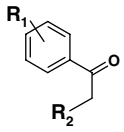
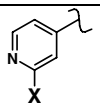
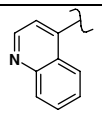
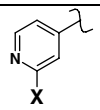
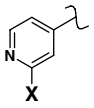
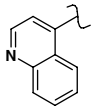
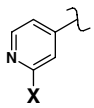
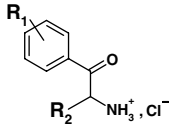
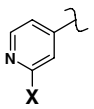
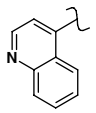
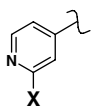
2. Results and discussion

Our general synthetic pathway is briefly shown in Scheme 1 starting from a number of ketones **3** which were produced by either deprotonating 2-halogeno-4-methylpyridine or 4-methylquinoline, and consecutively reacting them with different ethyl fluorobenzoates **2**. The main feature of the reactivity of alkylpyridines and analogous alkylquinolines is the deprotonation of the alkyl group at the carbon adjacent to the hetero ring. In this regard, it is common knowledge that alkyllithiums selectively deprotonate α-methyl groups whereas amide bases prefer to produce the more stable γ-anion.[11] The facility of deprotonation of the α- and γ-isomers is related to the mesomeric stabilization of the anion involving the ring nitrogen. Former methods characteristically realized such γ-deprotonation/substitution operations via LDA at −78 °C, with the application of the expensive Weinrebamides as the corresponding electrophiles.[5,6] We performed this fundamental step according to Thompson's protocol[12] using sodium bis(trimethylsilyl)amide (NaHMDS) in THF at moderate temperatures using easily accessible fluoro-substituted benzoic acid esters, thus avoiding the disadvantages of low reaction temperature, the requirement for a strictly inert atmosphere, and lengthy reaction time. Herein, ethyl esters **2** provided better results than methyl esters. After deprotonation of 2-halogeno-4-methylpyridine or 4-methylquinoline at 0 °C and the addition of the corresponding ethyl fluorobenzoates, the mixtures were allowed to come slowly to room temperature to complete the nucleophilic substitutions. In every case, the total reaction time was limited to 2.5 h. After quenching the reactions with diluted aqueous HCl, the organic layer was separated and almost pure and previously reported halogenpyridine ketones[9,13] **7**–**9** and **11** could be isolated from THF as white to yellowish solids or viscous brownish oils in up to 87% yield (Table 1). While 1-(4-fluorophenyl)-2-(2-fluoropyridin-4-yl)ethanone (**7**) as well as the analogous chloro- and bromopyridine derivatives **8** and **9** could be obtained crystalline by submerging the obtained residue in *tert*-BME followed by filtration of the precipitate, the corresponding 3-trifluoromethylphenyl compound **11** remained gelatinous. In contrast, the novel 1-(4-fluorophenyl)-2-quinolin-4-yl-ethanone (**10**) slowly crystallized as a pure white fluffy substance from the water phase (open beaker, a few days, 100%). If necessary, purification of the ethanones was conducted by extracting the crude material with hot hexane. After cooling, the pure products separated as voluminous needles. Preparation of the α-oximinoketones **12**–**14**[9] as well as **15** and **16** was derived from ethanones **7**–**11** by stirring with an excess (3 equiv) of sodium nitrite in acetic acid at room temperature. Addition of water led to precipitation of the product as a fine white powder. A positive reaction course was always indicated by the release of nitrogen gas. In each case, the preferred oxime regioisomer was formed as a single product in line with reported data (TLC and ^{1}H NMR).[9] Finally, the oximes exemplified by **4** were reduced to amines **17**–**19**,[9] **20**, **21** by vigorous shaking with Pd–C under hydrogen gas in HCl/2-propanol at atmospheric pressure and room temperature. Completion of the reaction was monitored by TLC. 2-Halogenopyridines reacted with ethanol under acidic conditions, but not with sterically more demanding isopropanol. Bromopyridine derivative **14**,[9] however, underwent a hydrogenolytic cleavage yielding pure unsubstituted pyridine **19**. To our surprise, the potential concomitant reduction of the vicinal carbonyl group was never detected under these conditions. The desired products could be isolated quantitatively as fine powdered hydrochlorides. Table 1 gives an overview of the synthetic routes to these key intermediate α-amino ethanones **5**. The final target compounds **6** as specified in Table 2 were prepared from **5** using an extended



Scheme 1. Optimized synthesis of 2-thioimidazoles. Reagents and conditions: (i)[12] NaHMDS 2.0 M in THF, 2-halogeno-4-methylpyridine or 4-methylquinoline, THF, 0 °C then rt; (ii) $NaNO_2$, glacial acetic acid; (iii) H_2, Pd–C 10%, 1 atm, 2-propanolic hydrogen chloride, rt; (iv) DMF, methyl-/ethyl-/benzylthiocyanate, reflux.

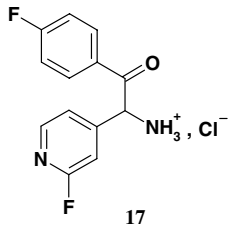
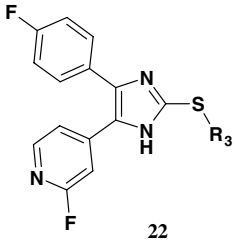
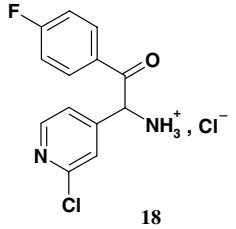
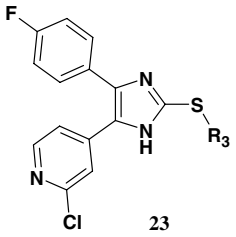
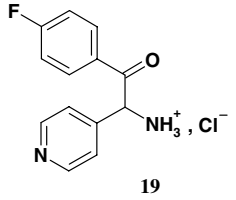
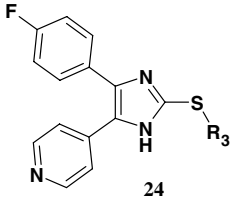
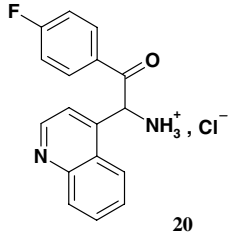
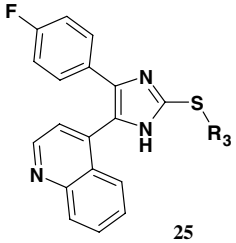
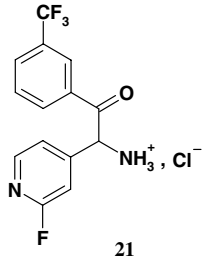
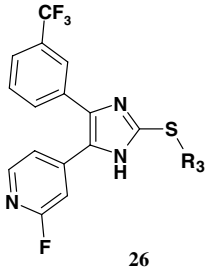
Table 1. Summarization of the synthetic route to key intermediate amino ethanone hydrogen chlorides[a]

	R_1	4-Fluoro-			4-Fluoro-	3-Trifluoromethyl-
	R_2					
	X	F	Cl	Br		F
Code	(Yield)	**7** (86%)	**8** (84%)	**9** (87%)	**10** (100%)	**11**
	Cond.	a	a	a	a	a
	R_2					
	X	F	Cl	Br		F
Code	(Yield)	**12** (84%)	**13** (91%)	**14** (82%)	**15** (62%)	**16** (82%)[b]
	Cond.	b	b	b	b	b
	R_2					
	X	F	Cl	H		F
Code	(Yield)	**17** (100%)	**18** (100%)	**19** (100%)	**20** (100%)	**21** (100%)

[a] Reagents and conditions: (a) $NaNO_2$, glacial acetic acid; (b) H_2, Pd–C 10%, 1 atm, 2-propanolic hydrogen chloride, rt.
[b] Yield over 2 steps.

procedure of the Marckwald synthesis. Herein, α-amino ketones were originally condensed with KSCN to give imidazole-2-thiols. We have already reported using such 4,5-diaryl-imidazole-2-thiols for probing substituents in the 2 position of the imidazole.[14] Our idea was now to directly constitute 2-(aryl-)alkylsulfanyl-4,5-diaryl-imidazoles in a single step following the Asinger procedure,[15] reported for cyclization reactions of α-mercapto ketones. Moreover, we increased the overall yield compared to our former multi-step procedure. Initially we selected methyl, ethyl, and benzyl thiocyanate, to couple with the α-amino carbonyl salts. The resulting C^2–S-methyl- or benzyl-substituted imidazoles (Table 2) were already known to be good pharmacophores for p38 MAP kinase inhibition.[1,9,14] Additionally, the protocol of Ando[16] that permits a simple thiocyanate reagent preparation using inorganic-solid-supported potassium thiocyanate attracted our interest. All cyclizations were performed in DMF. In general, the α-amino ethanones were dissolved at room temperature in absolute DMF under argon and to this solution a 2- to 2.5-fold excess of the liquid or solid thiocyanate was directly added in one portion by rapid injection (**22a**,[9] **22b**, **23a**,[9] **23b**, **24**,[9] **25**, **26a**, and **26b**) or per hopper, respectively (**22c**,[9] **23c**,[9] **26c**). Typically the primary bright orange mixtures turned to intensive red when warming to reflux temperature (160 °C, 45 min). Completion of the reactions was indicated by the color change of the refluxed solutions to orange from the initial red. The mixtures were allowed to cool slowly to room temperature and ice cold water was added. In many cases, a fine yellow to orange product precipitated (**22a**, **24**, **26a**) or an orange to brownish viscous mass (**22c**, **23a**) dropped out of the solution and was gathered (Table 2, variant A) and dried in vacuo over $CaCl_2$. Contrary to our expectation, the isolated residues of **22a**, **24**, and **26a** showed satisfactory analytical results and required no further purification. The raw products **22c** and **23a** could be solidified and obtained pure by washing with a little cold diethyl ether. Alternatively, the DMF/H_2O mixture was extracted with ethyl acetate and after evaporation of the solvents, the resulting oily crude residue was purified by column chromatography (**22b**, **23b**,**c**, and **26b**,**c**) (variant B) or preparative TLC (**25**) (variant C). As summarized in Table 2, isolated yields ranged from modest to excellent, and were dependent on the inserted thiocyanates as well as the provided aminoethanone hydrogen chlorides. For the resultant 2-methylsulfanylimidazoles, the yield

Table 2. Synthesis of 2-(aryl-)alkylsulfanyl imidazoles

α-Aminoketone	Product	Code	R_3	Variant[a]	Yield[b] (%)	GC–MS[c] (*m*/*z*)
 **17**	 **22**	**22a**	$-CH_3$	A	77	303 (M^+)
		22b	$-C_2H_5$	B	35	317 (M^+)
		22c	–Bn[d]	A	56[e]	379 (M^+)
 **18**	 **23**	**23a**	$-CH_3$	A	68[e]	320 (M^+)
		23b	$-C_2H_5$	B	32	333 (M^+)
		23c	–Bn	B	49	395 (M^+)
 **19**	 **24**	**24**	$-CH_3$	A	30	285 (M^+)
 **20**	 **25**	**25**	$-CH_3$	C	25	335 (M^+)
 **21**	 **26**	**26a**	$-CH_3$	A	84	353 (M^+)
		26b	$-C_2H_5$	B	11	367 (M^+)
		26c	–Bn	B	42	429 (M^+)

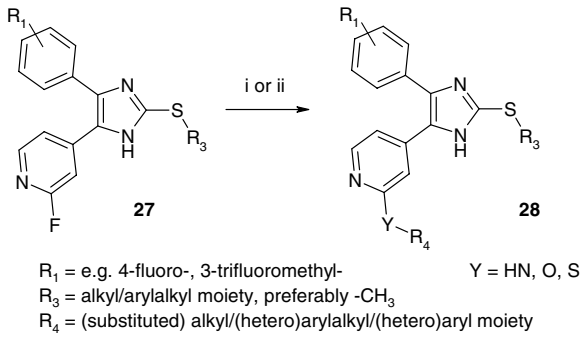
[a] Variant A: Precipitation with H_2O and if required, washing the crude product with a little cold diethyl ether; Variant B: Extracting with ethyl acetate, then column chromatography (SiO_2 60, dichloromethane/ethyl acetate, 1/1); Variant C: Extracting with ethyl acetate followed by preparative TLC (RP-18 F_{254}, methanol/H_2O, 9/1).

[b] Conditions: DMF, 160 °C, 45 min.

[c] GC/MS analyses were carried out on a HP 6890 series GC-system equipped with a HP-5MS capillary column and a HP 5973 mass selective detector (70 eV).

[d] Bn = Benzyl = $-CH_2Ph$.

[e] Contains traces of side products (GC).



Scheme 2. Nucleophilic aromatic displacement of the fluorine at the pyridine moiety. Reagents and conditions: (i) Excess of aliphatic or aromatic primary or secondary amine, neat, reflux or 160 °C; (ii) NaH, DMF, excess of aliphatic or aromatic alcohol or thioalcohol, 160 °C.

was generally high when the pyridine moiety was halogen substituted. The fluoropyridylimidazole compounds **22a–c** and **26a–c** can be used for further substitutions with various aromatic, heteroaromatic or aliphatic amines, alcohols, or thioalcohols to optimize p38 inhibition activity or to decrease CYP interaction as described elsewhere[9,17,18] (Scheme 2).

3. Conclusions

In summary, two major synthetic achievements were realized. First, the construction of fundamental ethanones **2** was simplified by conducting the reaction at moderate temperature and with less strictly inert conditions. Reaction time was drastically minimized while yields were constantly high (84–100%) as compared to our already reported method that suffered from irregular yields (5–99 %). The procedure could be applied to diverse starting compounds (Table 1). Moreover, we demonstrated that a series of alkyl- or arylalkyl thiocyanates are convenient cyclization reagents for the direct production of 2-(aryl-)alkylsulfanyl imidazoles in moderate to excellent yields (up to 84%) from several amino ethanone hydrogen chlorides. Preparation of the analogous 2-thioimidazoles by former multi-step procedures only afforded, at maximum, 39% yield (last step). Fluoro- and chloropyridine moieties are compatible with the process. Only in the bromopyridine derivative **14**, was bromine hydrogenolytically cleaved during the reduction step. The optimized thioimidazole synthesis also afforded the production of some new derivatives (**22b**, **23b**, **25**, **26a–c**) which can be used either as test candidates or as intermediates for further synthetic optimizations. In most cases, when applying methylthiocyanate as the cyclization reagent, the desired, almost pure products could be directly precipitated from DMF. In using ethyl- or benzylrhodanide, a subsequent extraction and purification was casually necessary. In contrast to former thioimidazole syntheses and in comparison to already available data, this new cyclization reaction accelerates and improves imidazole building while increasing total yields.

Supplementary data

Selected experimental procedures and spectroscopic data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.147.

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