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First synthesis and further functionalization of 7-chloro-imidazo[2,1-*b*][1,3]thiazin-5-ones

Clemens Lamberth *, Florian Querniard

Syngenta Crop Protection AG, Research Department, Schaffhauserstrasse 101, CH-4332 Stein, Switzerland

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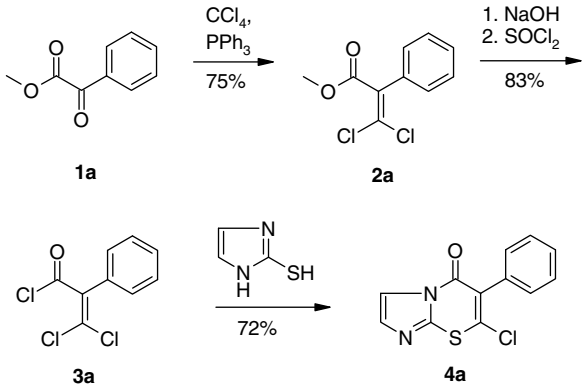
Abstract

A convenient four-step preparation route to novel 7-chloro-imidazo[2,1-*b*][1,3]thiazin-5-ones is presented, starting from methyl phenylglyoxylate. A unique feature of this synthesis is a heterocyclization strategy, in which a halogen atom is introduced already during the ring closure. 7-Chloro-6-phenyl-imidazothiazinones with a broad range of various substituents in the phenyl and imidazole moieties are obtainable by this method, as well as different chlorinated triazolothiazinones. The chloro function can be easily replaced in nucleophilic substitution reactions by amino, alkoxy and arylthio groups as well as by a fluoro atom.

Keywords: Heterocycle; Heterocyclization; Imidazole; Thiazine; Imidazothiazine

Although a few syntheses of imidazo[2,1-*b*][1,3]thiazin-5-ones have been described already,[1] so far there is no example for a derivative with a halogen substituent in position 7. Because of the known antibacterial[2] and fungicidal[3] activity of imidazo[2,1-*b*]thiazinones and the proven positive influence of halogen substituents on the efficacy of biological active compounds,[4] we decided to prepare a series of 7-chlorinated imidazo[2,1-*b*][1,3]thiazin-5-ones.

Usually in thiazine chemistry, the introduction of a chloro substituent into the ortho position of the ring sulfur is performed either by radical[5] or by ionic[6] halogenation of an unsubstituted ring carbon atom or by nucleophilic displacement of a hydroxy group.[7] In all the cases, the thiazine ring is formed before the halogen atom is introduced. Only one example can be found in the literature, in which ring closure to thiazinones and chlorination have been achieved in one step using different 3,3-dichloroacryloyl chlorides as key intermediates.[8] With regard to an efficient and atom-economic synthesis, we planned to apply a similar approach to the synthesis of 7-chloro-imidazo[2,1-*b*][1,3]thiazin-5-ones. In this connection, 3,3-dichloro-2-phenylacryloyl chloride (**3a**)[9] seemed to be an appropriate intermediate for such compounds (Scheme 1). It could be easily prepared by Corey–Fuchs type dichlorovinylation of methyl phenylglyoxylate (**1a**),[10] subsequent ester saponification and acid chloride formation. This compound was directly transformed into the formerly unknown imidazo[2,1-*b*][1,3]thiazin-5-one **4a** by condensation with 2-mercaptoimidazole (Scheme 1).[11] Hereby, one of the



Scheme 1. Four-step synthesis of 7-chloro-6-phenyl-imidazo[2,1-*b*]-[1,3]thiazin-5-one (**4a**).

* Corresponding author. Tel.: +41 61 323 2373; fax: +41 61 323 8726.
E-mail address: clemens.lamberth@syngenta.com (C. Lamberth).

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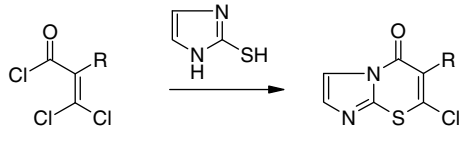
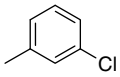
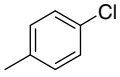
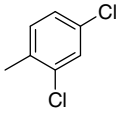
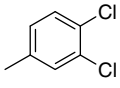
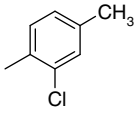
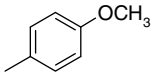
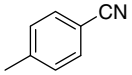
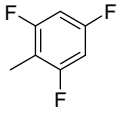
Table 1
Synthesis of 7-chloro-6-aryl-imidazo[2,1-*b*][1,3]thiazin-5-ones with different substituents in the phenyl ring



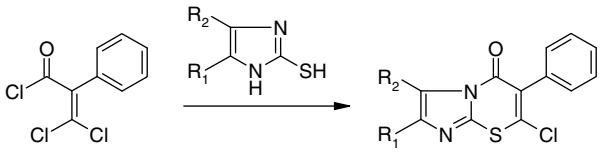
3a-i **4a-i**

Entry	R	Yield (%)	Mp (°C)
a		72	116–117
b		69	101–104
c		75	165–166
d		56	181–182
e		68	118–119
f		53	167–168
g		73	152–155
h		64	184–187
i		57	117–120

vinylic chlorine atoms in **3a** is substituted during the ring closure, the other remains in the molecule.

By the application of this heterocyclization method, several imidazo[2,1-*b*][1,3]thiazin-5-ones with a broad variety of different substituents in the phenyl ring were synthesized (Table 1). The heterocyclization is possible in the presence of electron-donating as well as electron-withdrawing substituents in *ortho*-, *meta*- or *para*-positions of the phenyl ring. The yields were generally between 50% and 75%, the lowest yields were usually obtained in those reactions of 3,3-dichloro-2-arylacryloyl chlorides with *ortho*-substituents in the phenyl moiety.

Table 2
Synthesis of 7-chloro-6-phenyl-imidazo[2,1-*b*][1,3]thiazin-5-ones with different substituents in the imidazole ring



3a **4a, k-m**

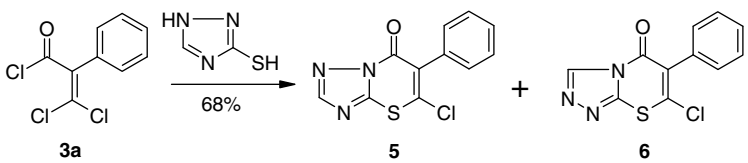
Entry	R_1	R_2	Yield (%)	Mp (°C)
a	H	H	72	116–117
k	Me	Me	74	182–183
l	Ph	Ph	63	Oil
m	CH=CH–CH=CH		70	197–198

Also the synthesis of various 7-chloro-6-phenyl-imidazo[2,1-*b*][1,3]thiazin-5-ones with different substituents in the imidazole ring was possible (Table 2). The application of 2-mercaptobenzimidazole as the reaction partner of 3,3-dichloro-2-phenylacryloyl chloride (**3a**)[9] led to the unique tricyclic chloro- and phenyl-substituted 1-thia-4a,9-diazafluorenone **4m**.

When 3-mercapto-1,2,4-triazole was used instead of 2-mercaptoimidazole, triazolothiazinones were obtained in the heterocyclization reaction (Scheme 2). In the conversion with 3,3-dichloro-2-phenylacryloyl chloride (**3a**),[9] the two different isomers **5** and **6** were formed in equal amounts, depending on which triazole ring nitrogen reacted in the cyclization.

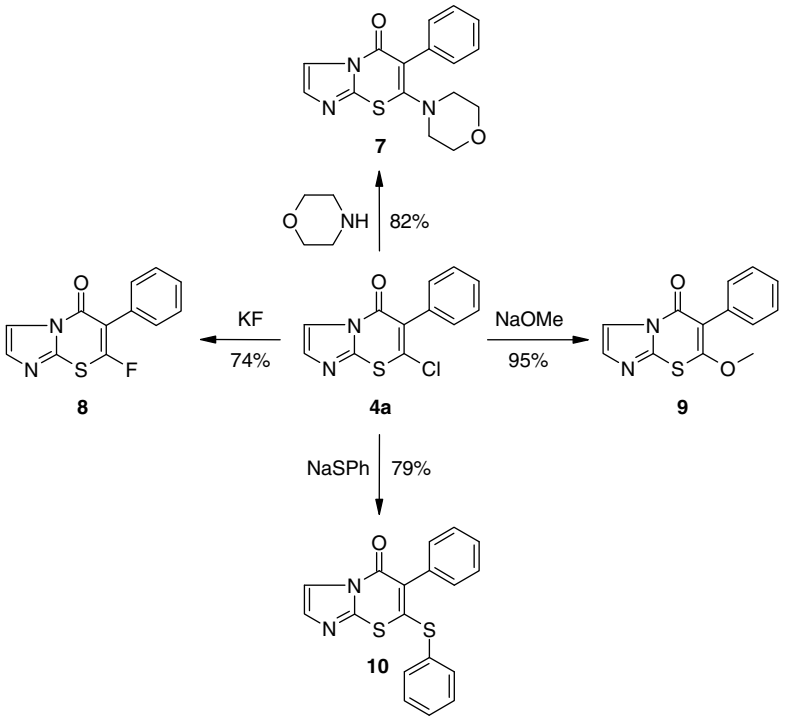
The 7-chloro-6-aryl-imidazo[2,1-*b*]thiazin-5-ones **4a**–**m** are absolutely stable at room temperature for a very long time, but could be easily transformed into novel compounds due to the leaving group character of its chloro function. Some possible derivatizations are the exchange against a fluoro atom to afford **8** or the nucleophilic substitution with amines, alkoxides or thiolates, delivering **7**, **9** and **10** (Scheme 3).

In conclusion, we have developed a concise and efficient route to 7-chloro-6-aryl-imidazo[2,1-*b*][1,3]thiazin-5-ones. Their chloro atom can be easily replaced through various nucleophilic substitutions. Also 5-chloro-6-aryl-triazolo-[5,1-*b*]thiazin-7-ones and 7-chloro-6-aryl-triazolo[3,4-*b*]-thiazin-5-ones can be obtained by this method.



3a **5** **6**

Scheme 2. Synthesis of 5-chloro-6-phenyl-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-one (**5**) and 7-chloro-6-phenyl-[1,2,4]triazolo[3,4-*b*][1,3]thiazin-5-one (**6**).



Scheme 3. Further transformations of 7-chloro-6-phenyl-imidazo[2,1-*b*][1,3]thiazin-5-one (**4a**).

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11. *Representative procedure*: *N*,*N*-Diisopropylethylamine (Hünig's base, 1.6 g, 12.5 mmol) was added to a solution of 2-mercaptoimidazole (1.1 g, 11 mmol) in 20 ml of dichloromethane at room temperature. Subsequently, a solution of 3,3-dichloro-2-phenylacryloyl chloride[8] (**3a**, 2.4 g, 11 mmol) in 5 ml of dichloromethane was added dropwise while maintaining the temperature at 15–20 °C. The resulting mixture was stirred for 16 h at room temperature, taken up in water and extracted with dichloromethane. The combined organic phases were washed with brine, dried over magnesium sulfate and evaporated. The residue was purified either by crystallization from diethyl ether or by chromatography on a silica gel, using ethyl acetate–heptane 1:3 as eluent to deliver 7-chloro-6-phenyl-imidazo[2,1-*b*][1,3]thiazin-5-one (**4a**, 2.1 g, 7.9 mmol, 72%). Mp: 116–117 °C. ^{1}H NMR (ppm, $CDCl_3$): δ 7.34 (d, 2H), 7.43 (s, 1H), 7.48–7.55 (m, 3H), 7.99 (s, 1H). ^{13}C NMR (ppm, $CDCl_3$): δ 114.8, 115.3, 117.9, 118.6, 120.1, 124.5, 126.4, 127.2, 132.0, 139.7, 141.4, 157.5. HRMS (*m*/*z*): calcd for $(C_{12}H_7ClN_2OS+H)^+$: 263.7227; found: 263.7231.