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Synthesis of New [1,2,3]Triazoles and 1*H*-Tetrazoles *via* Reactions of 3,(5)-(Di)chloro-2*H*-1,4-(benz)oxazin-2-ones with Diazocompounds or Sodium Azide.

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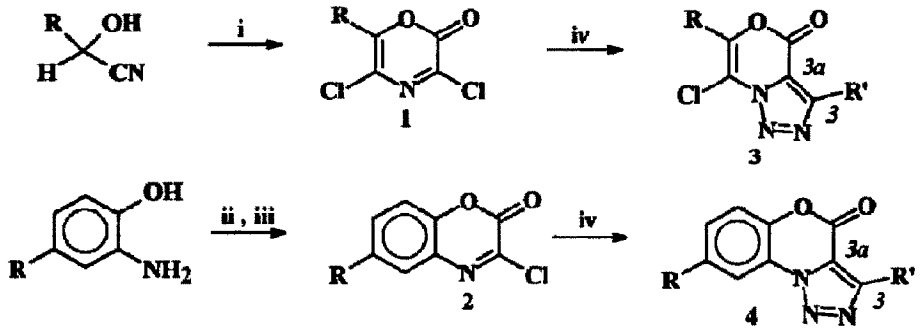
Abstract: Treatment of 3,(5)-(di)chloro-2*H*-1,4-(benz)oxazin-2-ones with diazo compounds or sodium azide yields bi(tri)cyclic compounds which can be converted into [1,2,3]triazoles or 1,5-disubstituted tetrazoles via reactions with nucleophiles as methanol, water and amines.

Recently, a new one step synthesis of 3,5-dichloro-2*H*-1,4-oxazin-2-ones **1** was developed in our laboratory.[1a,b] These compounds turned out to be outstanding starting materials in the synthesis of pyridines[2] and oxazoles.[3]

In this communication, we wish to describe the use of compounds **1** and the analogues **2** in the synthesis of specifically substituted [1,2,3]triazoles which are characterised by a carboxylic group in 5-position and an α-chloro ketone substituent or an *ortho*-hydroxy phenyl group at N-1. These method yielding a peculiar substitution pattern for the title compounds is a quite simple and undescribed approach which makes use of a selective reaction of the imidoyl chloride function followed by cleavage of the lactone.



Scheme 1

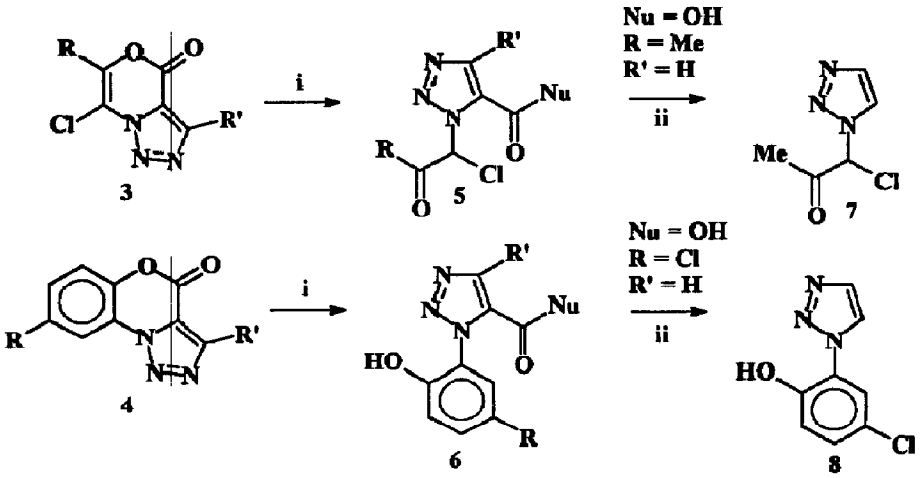
Reagents and conditions: i, oxalyl chloride (4 equiv.), NEt_3.HCl (0.5 equiv.), chlorobenzene, 4 h, 90 °C; ii, oxalyl chloride (1.4 equiv.), chlorobenzene, 3 h, 120 °C; iii, DMF (0.01 equiv.), $SOCl_2$ (1.4 equiv.), 1 h, 120 °C; iv, excess of diazo compound, ether, 4 d, 4 °C (when diazoethane or diazopropane was used, the initial temperature was -78 °C)

In step 1 an ethereal solution of compounds 1 and 2 (easily prepared by reaction of oxalyl chloride and the appropriate cyanohydrins or *ortho*-amino phenols[4]) was treated with excess of diazo compound. By selective attack on the imidoyl chloride function followed by rapid ring closure (via diazoimine-triazole equilibrium) [1,2,3]triazolo[5,1-c][1,4]oxazin-4-ones 3a-c and [1,2,3]triazolo[5,1-c][1,4]benzoxazin-4-ones 4a-c were obtained in moderate yields (Table 1). The diazoimine-triazole equilibrium is well known in the literature.[5a,b] However, the absence of IR absorptions around 2100 cm^{-1} in compounds 3 and 4 points out to their triazole structure.

Table 1: Yield of the Intermediate [1,2,3]Triazolo[5,1-c][1,4](benz)oxazin-4-ones 3a-c and 4a-c.

Compound	R	R'	Yield (%)
3a	Me	H	91
3b	2,6-Cl_2Ph	Me	unstable
3c	Ph	H	81
4a	Cl	H	68
4b	Cl	Et	41
4c	H	H	75

The triazole structure of the stable compounds 3a,c and 4a-c has been secured by spectral data. The triazole proton appears in the region between 8.5 and 8.9 ppm (^{1}H NMR); the triazole carbon atoms absorb at 123 (± 1) ppm (C_{3a}) and at 136.5 (± 1) ppm (C_3). In case of 4b however the signals are found at 118 ppm (C_{3a}) and 155 ppm (C_3) (^{13}C NMR). IR spectra show intensive absorptions from 1750 to 1780 cm^{-1} due to the lactone carbonyl stretching. Mass spectral analyses indicate significant loss of N_2 and CO.



Scheme 2

Reagents and conditions: i, in case of 5a, 5b, 6a and 6b: methanol, 12 h, reflux; 5c and 6c: diethyl amine, 1 h, r.t.; 6d: propyl amine, 1 h, r.t. 6e: ethyl acetate, 1.1 equiv. aniline, 4 d, reflux; ii, chlorobenzene, 1 d, 130 °C.

The second step of our procedure is the cleavage of the lactone function in **3** and **4** with various nucleophiles such as alcohols, amines and water (Table 2). Refluxing **3a**, **4a** and **4b** overnight in methanol provided the triazole esters **5a**, **6a** and **6b** in good yield. Compound **5b** was obtained in 25% overall yield after reaction with methanol of the crude mixture of the less stable **3b** (which could not be purified). When water was used as nucleophile in the reaction with **3a** and **4a**, unstable acids were formed which could be thermolysed into to the N-substituted triazoles **7** and **8**.

Furthermore, cleavage of the lactone function in **3a** and **4c** has been accomplished at room temperature with diethyl amine; this led to the [1,2,3]triazole-carboxamides **5c** and **6c**. Primary amines could also be used. Treatment of **4b** with propyl amine at room temperature yielded **6d**. Reflux temperature was needed to open the lactone of **4a** with aniline to provide the triazole **6e**.

Table 2: Yield of the [1,2,3]Triazoles **5a-e** and **6a-e**.

Compound	R	R'	Nu	Yield (%)
5a	Me	H	OMe	95
5b	2,6-Cl_2Ph	Me	OMe	25*
5c	Me	H	NEt_2	87
6a	Cl	H	OMe	75
6b	Cl	Et	OMe	79
6c	H	H	NEt_2	60
6d	Cl	Et	NHProp	76
6e	Cl	H	NHPh	59

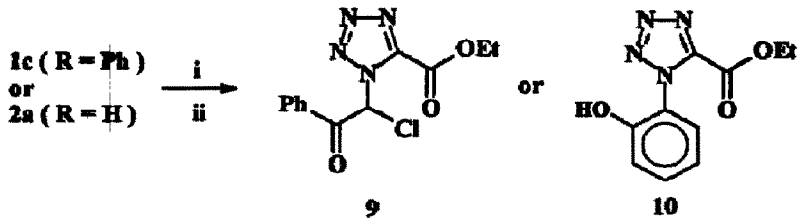
* overall yield starting from **3b**

The final triazoles are characterized by the following spectral data comparable with these of known analogues. The [1,2,3]triazoles **5** and **7** possess an α-chloro ketone substituent on N-1. Their ^{1}H NMR absorptions are found around 7.2 (± 0.1) ppm for **5a** and **5c** and 8.4 ppm for **5b**; ^{13}C-signals appear around 70 (± 1) ppm. The carbonyl C-atom gives a signal between 188 and 194 ppm. The *ortho*-hydroxy phenyl substituent at N-1 in the [1,2,3]triazoles **6** and **8** is characterized by a signal at 151 ppm (^{13}C NMR) and a broad band from 2500 cm^{-1} to 3300 cm^{-1} in IR. The CH of the triazole ring of **5a,c** and **6a,c,e** appears at 8.2 (± 0.3) ppm (^{1}H NMR) and 134 (± 4) ppm (^{13}C NMR). In all IR spectra intensive absorptions can be found between 1650 cm^{-1} and 1750 cm^{-1} due to the carbonyl of the α-chloro ketone and the ester or the amide group. Mass spectral data show easy loss of CO and N_2.

This method seems to be an excellent procedure for the synthesis of new, unknown [1,2,3]triazoles **5** - **8**. 1,3-Dipolar cycloaddition of azides to unsymmetrical acetylenic compounds gives mainly the 4-substituted isomer whereas the 5-isomer is selectively obtained by our approach. Other methods providing an electron withdrawing group in 5-position are limited by low yields and complicated multistep reactions.[6] An additional peculiarity is the generation of the α-chloro ketone or *ortho*-hydroxy phenyl substituent on N-1.

Furthermore, applying a comparable methodology on **1c** (R=Ph) and **2a** (R=H) with sodium azide, 1,5-disubstituted tetrazoles **9** and **10** could also be made accessible after cleavage of the lactone in the intermediate tetrazolo(benz)oxazinones with ethanol.

The structure of the tetrazoles was confirmed by the following (partial) spectral data. **9**: Yield: 70%, ^{1}H NMR: 8.3 ppm (s, 1H, CHCl), 4.5 ppm (m, 2H, CH_2-CH_3). 1.3 ppm (t, 3H, CH_2-CH_3); ^{13}C NMR: 155.9 ppm (O-C=O), 184.7 ppm (C=O), 66.2 ppm (CHCl); IR: 1720 cm^{-1} (C=O). **10**: yield: 68%, ^{1}H NMR: 7.9 ppm (s, 1H, OH), 4.3 ppm (m, 2H, CH_2-CH_3). 1.2 ppm (t, 3H, CH_2-CH_3); ^{13}C NMR: 156.8 ppm (O-C=O), 151.8 ppm (C_{ar}-OH); IR: 3117 cm^{-1}(OH), 1750 cm^{-1} (C=O).



Scheme 3

Reagents and conditions: **9**: i, DMF, NaN_3 (1.1 equiv.), 2 h, r.t.; ii, ethanol, 10 min, reflux.
10: i, CH_3CN, NaN_3, (2 equiv.), 1h, 50°C; ii, ethanol, 12 h, reflux.

We can conclude that the described methodology opens a new and simple way for specifically substituted [1,2,3]triazoles and also 1,5-disubstituted tetrazoles. The latter can be generated by other methods described in the literature[7] however none of these are suitable for the introduction of an α-chloroketone or *o*-hydroxyaryl substituent on N-1.

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