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An unprecedented rearrangement of salicylanilide derivatives: imidazolinone intermediate formation

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ABSTRACT

The preparation of new prodrug forms of anti-tuberculosis active salicylanilide esters with amino acids led to an unexpected rearrangement. The isolation and the structure determination of 2-(5-chloro-2-hydroxyphenyl)-3-(3-chlorophenyl)-5-substituted-3,5-dihydro-4*H*-imidazol-4-ones unambiguously confirm one of the two proposed reaction mechanisms.

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Multi-drug resistance to antimicrobial agents is an unavoidable side effect of their use and goes hand-in-hand with the relentless drive of bacterial evolution. Ongoing combat against drug-resistant bacteria leads to the search for new types of active molecules with different or novel mechanisms of action. Salicylanilides are promising candidates for this purpose, due to their wide range of pharmacological activity, including antifungal and antibacterial.[1,2] In a series of publications, Waisser and co-workers described their significant in vitro antimycobacterial activity against *Mycobacterium tuberculosis* as well as against the non-tubercular strains *Mycobacterium avium* and *Mycobacterium kansasii*.[3–5] The presence of phenolic hydroxy groups seems to be necessary for the activity of these compounds,[6] but also converts them into non-bioavailable drugs.

In order to improve physico-chemical and pharmacokinetic properties, including metabolic stability, a new prodrug form of salicylanilide was proposed. Substituted salicylanilides **1** were esterified with different N-protected amino acids. In the course of our research, we found that *N*-benzyloxycarbonyl glycine **1** (R^3 = H) or (*S*)-alanine (R^3 = CH_3), when esterified with salicylanilides **2** (R^1 = 5-Cl, R^2 = 4-Cl, 4-Br, 4-CF_3, 3-Cl) gave cyclic seven-membered benzoxazepine-2,5-diones **3**,[7] while other N-protected amino acids **2**, such as (*R*)- or (*S*)-phenylalanine or valine, afforded the required esters **4** in high yields[8,9] (Scheme 1).

Acidic N-deprotection of **4** with hydrogen bromide in acetic acid gave the corresponding hydrobromide salts **5**. Subsequent liberation of the amino group with triethylamine under anhydrous conditions yielded the rearranged hydroxy-*N*-(phenylamino)-oxo-alkylbenzamide (diamide) **6** (Scheme 2). The rearrangement also occurs with unsubstituted salicylanilides or with electron-activating methyl (**6f**) or methoxy groups on the aniline moiety (**6e**). This process is not limited to salicylanilide esters of Cbz-protected amino acids. We have used Boc-protected valine and the Leuch anhydride of phenylalanine[7] for esterification, and the appropriate salicylanilide esters, gave after N-deprotection, the rearranged diamides which were isolated and characterized. A series of compounds **6a**, **b**, **d**–**f** were prepared (Table 1).

In a previous publication[7], we proposed a possible mechanism for this rearrangement where the deprotected amino group immediately attacks the carbonyl of the amide and forms a cyclic seven-membered ester which is ring-opened by the action of the released aniline to produce the diamide.[7]

With the aim of confirming the above-proposed mechanism, we have carried out a number of experiments where activated anilines bearing a stronger nucleophilic substituent at position 4, were added to the reaction mixture. No rearranged diamides containing the added anilines were isolated, only the product containing the original aniline moiety. Therefore, an alternative mechanism involving reorganization of the molecule without liberation of the aniline moiety was investigated. We report in this Letter the elucidation of this mechanism.

The free amino group attacks the amidic carbonyl and the amidic nitrogen attacks the ester carbonyl to generate the bicyclic intermediate **7** which is spontaneously transformed into a five-membered hydroxyimidazolinone **8** which then ring-opens to form diamide **6** (Scheme 3).

Support for a five-membered imidazoline ring as an intermediate in this rearrangement came from our experimental results. During

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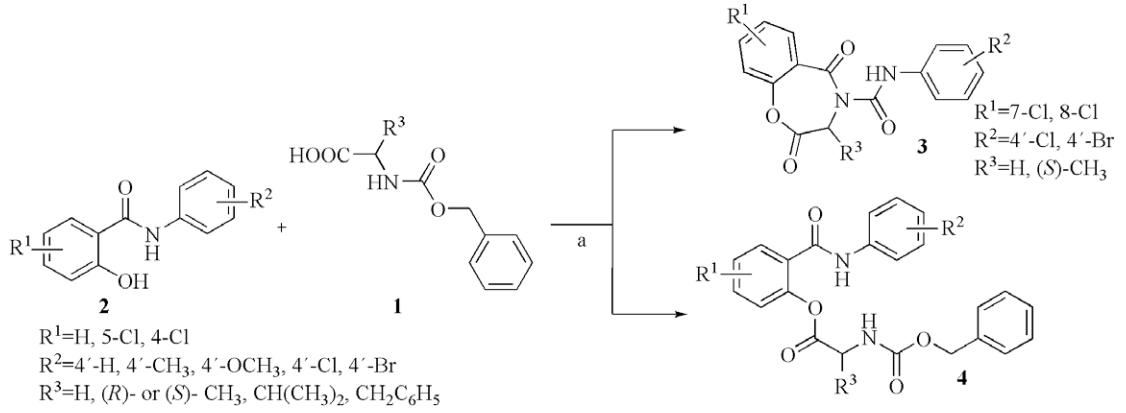
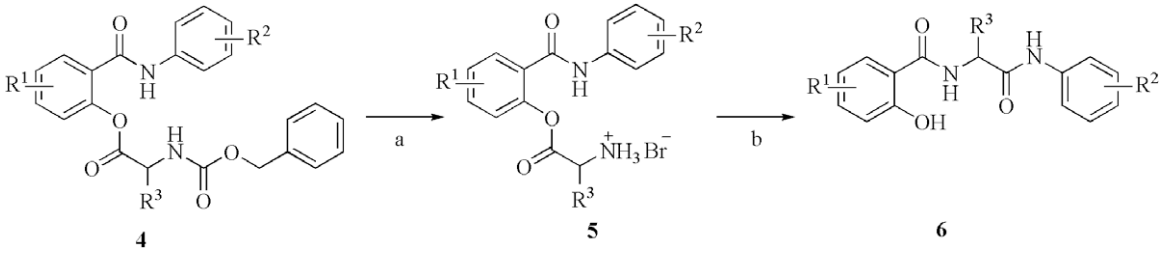
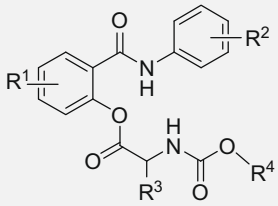
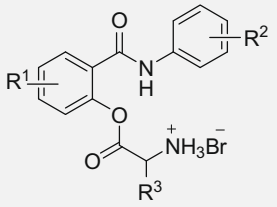
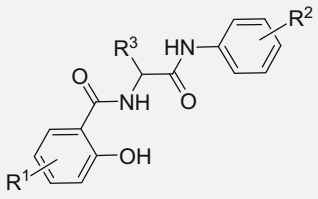


Scheme 1. Synthesis of benzoxazepine-2,5-diones **3** or Cbz-amino acids esters **4**. Reagents and condition: (a) DCI, DMF, −15 °C.

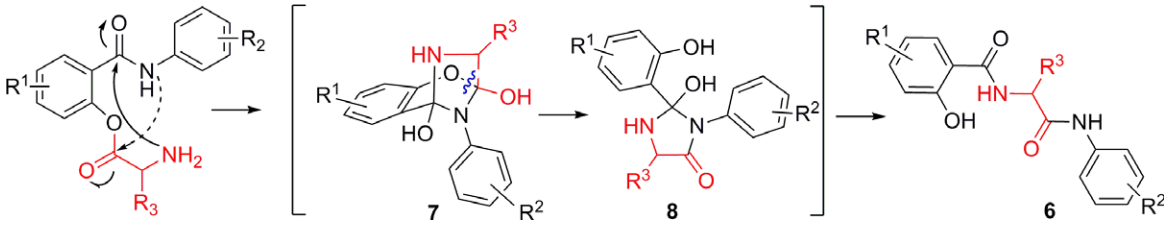


Scheme 2. Unexpected rearrangement of amino acid esters. Reagents: (a) HBr, CH_3COOH; (b) Et_3N.

Table 1
List of prepared compounds

Product	R^1	R^2	R^3	R^4	
	**4a**	4-Cl	3-Cl	$-CH(CH_3)_2$	$-CH_2C_6H_5$
	4b	4-Cl	3-Cl	$-CH_2C_6H_5$	$-CH_2C_6H_5$
	4c	4-Cl	3-Cl	$-CH(CH_3)_2$	$-C(CH_3)_3$
	4d	H	4-Cl	$-CH(CH_3)_2$	$-CH_2C_6H_5$
	4e	H	4-OCH_3	$-CH(CH_3)_2$	$-CH_2C_6H_5$
	4f	H	4-CH_3	$-CH(CH_3)_2$	$-CH_2C_6H_5$
	**5a**	4-Cl	3-Cl	$-CH(CH_3)_2$	
	5b	4-Cl	3-Cl	$-CH_2C_6H_5$	
	5d	H	4-Cl	$-CH(CH_3)_2$	
	5e	H	4-OCH_3	$-CH(CH_3)_2$	
	5f	H	4-CH_3	$-CH(CH_3)_2$	
	**6a**	5-Cl	3-Cl	$-CH(CH_3)_2$	
	6b	5-Cl	3-Cl	$-CH_2C_6H_5$	
	6d	H	4-Cl	$-CH(CH_3)_2$	
	6e	H	4-OCH_3	$-CH(CH_3)_2$	
	6f	H	4-CH_3	$-CH(CH_3)_2$	
	**9a**	5-Cl	3-Cl	$-CH(CH_3)_2$	
	9b	5-Cl	3-Cl	$-CH_2C_6H_5$	
	9d[a]	H	4-Cl	$-CH(CH_3)_2$	
	9e[a]	H	4-OCH_3	$-CH(CH_3)_2$	
	9f[a]	H	4-CH_3	$-CH(CH_3)_2$	

[a] Compound was not isolated, molecular weights were detected by GC–MS.



Scheme 3. Proposed mechanism for the rearrangement.

purification of the diamide **6a** by column chromatography, we isolated a side-product that proved to be a dehydrated form of this five-membered ring intermediate as a racemic mixture, 2-(5-chloro-2-hydroxyphenyl)-3-(3-chlorophenyl)-5-isopropyl-3,5-dihydro-4*H*-imidazol-4-one **9a** (Fig. 1). The structure of **9a** [R^1 = 5-Cl, R^2 = 3-Cl, R^3 = $CH(CH_3)_2$] was confirmed by MS, IR and 2D NMR and by X-ray crystallography. The same type of substituted 3,5-dihydro-4*H*-imidazol-4-one was isolated during the purification of **6b**, 5-benzyl-2-(5-chloro-2-hydroxyphenyl)-3-(3-chlorophenyl)-3,5-dihydro-4*H*-imidazol-4-one **9b** (Fig. 1) and its structure was determined by IR, ^{1}H NMR and ^{13}C NMR spectroscopy.

The negative and positive ion electrospray ionization (ESI) mass spectra of **9a** showed $[M]^+$ and deprotonated molecular ions $[M-H]^+$, respectively, which confirmed the molecular weight. The fragment ions observed in the MS spectra correspond to the suggested structure.

Additional structural determination of **9a** was made by ^{1}H NMR, ^{13}C NMR and ^{15}N NMR 2D experiments (gradient-selected (gs)-COSY, gs-HMQC, gs-HMBC) as well as by construction of a computer model using DFT (B3LYP/6-31G(d)). The IR, ^{1}H and ^{13}C NMR spectra were calculated based on this model.

Finally, compound **9a** was also studied by X-ray diffraction techniques. It crystallized in the monoclinic achiral space group $P2_1/c$. No important short contacts, π–π stacking or intermolecular H-bonds were present in the crystal lattice of **9a**. The ORTEP view of the structure of **9a** (Fig. 2, the unit cell plot is available in Supplementary data) shows the almost planar arrangement of the imidazolinone ring together with the phenyl rings mutually twisted by 70.6(2)°. The imidazolinone moiety contains two localized double bonds O1–C1 1.201(4) Å and N1–C2 1.275(4) Å (see Fig. 2), the lengths of which are in good agreement with the literature data[10] and similar ring systems found in the CSD database where related species contain very close,[11,12] bicyclic,[13] fused hetero,[14,15] or spirocyclic[16] systems. A similar structure has also been determined for imidazolinone rings coupled to a pyridine moiety and used as ligands in iron(III)[17] or copper(II)[18] complexes.

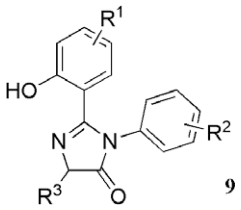


Figure 1. Isolated dehydrated reaction intermediates.

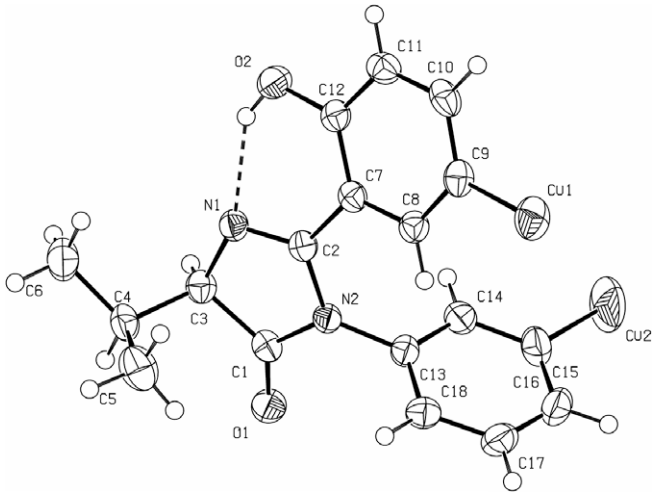


Figure 2. The ORTEP view of compound **9a**.

The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 695861.

In conclusion, we have elucidated the mechanism of the unexpected rearrangement of amino acid esters of salicylanilides. The isolated dehydrated form of the imidazolinone **9a** strongly supports the proposed mechanism for the formation of compounds **6**. The results of the X-ray study are in excellent agreement with the proposed structure and 2D NMR experiments. The above-mentioned rearrangement has provided new types of potential antitubercular compounds originating from salicylanilides. Their antimycobacterial activity is under investigation.

Acknowledgements

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Supplementary data

Supplementary data (general experimental information, experimental details, characterization data for compounds **4**–**6** and **9** and scans of NMR and MS spectra for compounds **9a** and **9b**, calculated IR-spectra, ^{1}H, ^{13}C NMR and 2D spectra of compound **9a** and the solid state study details for compound **9a** as well as Quantum-chemical calculations for **9a**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.084.

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