Synthetic Route for the Preparation of 2-Hydroxy-*N*-[1-(2-hydroxyphenylamino)-1-oxoalkan-2-yl]benzamides

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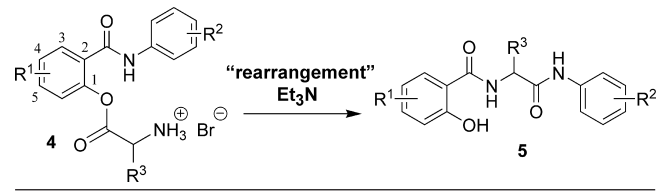
2-Hydroxy-*N*-[1-(2-hydroxyphenylamino)-1-oxoalkan-2-yl]benzamides **5** are original organic compounds containing two amidic functions and therefore are known as "diamides". In the recent past, our research group has found them to be potential antimicrobial agents,[1] presenting *in vitro* antimycobacterial activity in the range of 62.5 to 8 μmol/L against *Mycobacterium tuberculosis* (*M. tuberculosis*) and against some nontuberculosis strains, such as *M. avium* and *M. kansasii*. These compounds were also tested for their *in vitro* antifungal activity, showing interesting results for only a few members of the mentioned group of compounds (e.g., 0.49 μmol/L after 24/48 h for **5e** against *Trichophyton mentagrophytes* or **5bb** and **5cc** 3.9/7.81 and 1.95/3.9 μmol/L against *Candida krusei* strain). Furthermore, Shibasaki and co-workers[2] have published the synthesis of the diamide (*R*)-2-hydroxy-*N*-[1-(2-hydroxyphenylamino)-3-methyl-1-oxobutan-2-yl]benzamides (Scheme 1) as a promising ligand for the amination of succinimide in the catalytic asymmetric synthesis of AS-3201. The compound marked AS-3201 was identified as a structurally novel aldose-reductase inhibitor used in the treatment of diabetic disorders.[2]

In this context, the aim of this article was to describe an efficient and novel synthesis for this kind of "diamides". Initially, 2-hydroxy-*N*-(1-(oxo-(phenylamino)-alkan-2-yl)-benzamides **5** were prepared as a part of our ongoing search for new antituberculosis active molecules of salicylanilide esters.[3] Their synthesis started from several substituted salicylanilides (SAL) **1**, which were selected according to previous results showing high *in vitro* activity against *M. tuberculosis*.[4] They were routinely prepared using phosphorus trichloride (PCl_3) as a dehydrating agent in chlorobenzene (Ph−Cl), a well-known synthetic route. By using microwave irradiation (MW), the reaction time was shortened from several hours to minutes (see Scheme 2).[5]

The first step in the diamide **5** preparation was the esterification of SAL **1** with *N*-protected *R* or *S* amino acids (AA; neutral Gly, Ala, Val, Phe; basic Trp and unnatural cyclohexylalanine and *tert*-butyl glycine) by benzyloxycarbonyl (CBZ) or *tert*-butyloxycarbonyl (BOC) groups **2**. *N*,*N*′-Dicyclohexylcarbodiimide (DCC) was used as an optimal activation agent in dry dimethylformamide (DMF). The *N*-protected AA esters of SAL **3** were isolated in high purity by crystallization from ethyl acetate−hexane after filtration of *N*,*N*′-dicyclohexylurea and vacuum evaporation of DMF.[3a]

Table 1. List of Prepared Compounds **4** and **5**



compd	R^1	R^2	R^3	yield of **4** (%)	compd	yield of **5** (%)
4a	4-Cl	4-Cl	(*R*)-CH_3	89	**5a**	49[a]
4b	4-Cl	4-Cl	(*S*)-$CH(CH_3)_2$	97	**5b**	39[a]
4c	4-Cl	4-Cl	(*R*)-$CH(CH_3)_2$	92	**5c**	57[a]
4d	4-Cl	4-Cl	(*S*)-CH_2-phenyl	92	**5d**	44[a]
4e	4-Cl	4-Cl	(*R*)-CH_2-phenyl	95	**5e**	61[a]
4f	4-Cl	4-Br	(*R*)-CH_3	NP	**5f**	NP
4g	4-Cl	4-Br	(*S*)-$CH(CH_3)_2$	91	**5g**	56[a]
4h	4-Cl	4-Br	(*R*)-$CH(CH_3)_2$	93	**5h**	50[a]
4i	4-Cl	4-Br	(*S*)-CH_2-phenyl	97	**5i**	39[a]
4j	4-Cl	4-Br	(*R*)-CH_2-phenyl	93	**5j**	32[a]
4k	4-Cl	4,3-diCl	H	69	**5k**	27[b]
4l	4-Cl	4,3-diCl	(*S*)-CH_3	67	**5l**	23[b]
4m	4-Cl	4,3-diCl	(*R*)-CH_3	NP	**5m**	NP
4n	4-Cl	4,3-diCl	(*S*)-$CH(CH_3)_2$	87	**5n**	53[a]
4o	4-Cl	4,3-diCl	(*R*)-$CH(CH_3)_2$	89	**5o**	40[a]
4p	4-Cl	4,3-diCl	(*S*)-CH_2-phenyl	90	**5p**	23[b]
4q	4-Cl	4,3-diCl	(*R*)-CH_2-phenyl	90	**5q**	34[b]
4r	4-Cl	3-Cl	H	45	**5r**	32[b]
4s	4-Cl	3-Cl	(*S*)-CH_3	90	**5s**	43[a]
4t	4-Cl	3-Cl	(*R*)-CH_3	90	**5t**	88[c]
4u	4-Cl	3-Cl	(*S*)-$CH(CH_3)_2$	88	**5u**	46[a]
4v	4-Cl	3-Cl	(*R*)-$CH(CH_3)_2$	77	**5v**	39[a]
4w	4-Cl	3-Cl	(*S*)-CH_2-phenyl	96	**5w**	60[a]
4x	4-Cl	3-Cl	(*R*)-CH_2-phenyl	89	**5x**	75[c]
4y	4-Cl	4-CH_3	(*S*)-CH_3	96	**5y**	36[c]
4z	4-Cl	4-CH_3	(*S*)-$CH(CH_3)_2$	90	**5z**	89[c]
4aa	4-Cl	4-CH_3	(*S*)-CH_2-phenyl	90	**5aa**	65[c]
4bb	4-Cl	4-CH_3	(*R*)-CH_2-*1H*-indol-3-yl	59	**5bb**	95[c]
4cc	4-Cl	4-CF_3	(*S*)-$CH(CH_3)_2$	89	**5cc**	91[c]
4dd	4-Cl	4-CF_3	(*R*)-CH_2-*1H*-indol-3-yl	78.5	**5dd**	85[c]
4ee	4-Cl	3-CF_3	-CH_2-cyclohexyl	NI	**5ee**	76[c]
4ff	4-Cl	3-CF_3	-$C(CH_3)_3$	NI	**5ff**	69[c]
4gg	4-Cl	4-Br	-CH_2-cyclohexyl	97	**5gg**	82[c]
4hh	4-Cl	4-NO_2	(*S*)-$CH(CH_3)_2$	73	**5hh**	88[c]
4ii	4-Cl	4-OCH_3	(*S*)-$CH(CH_3)_2$	98	**5ii**	93[c]
4jj[6]	H	4-Cl	(*S*)-$CH(CH_3)_2$	89	**5jj**[6]	91[c]
4kk[6]	H	4-OCH_3	(*S*)-$CH(CH_3)_2$	93	**5kk**[6]	93[c]
4ll[6]	H	4-CH_3	(*S*)-$CH(CH_3)_2$	90	**5ll**[6]	93[c]
4 mm	5-Cl	4-Br	(*S*)-$CH(CH_3)_2$	92	**5 mm**	68[c]
4nn	5-Cl	4-Br	(*S*)-CH_2-phenyl	94	**5nn**	68[c]
4oo	5-Cl	4-Cl	(*S*)-CH_3	85	**5oo**	64[b]
4pp	5-Cl	4-Cl	(*R*)-CH_3	83	**5pp**	73[a]
4qq	5-Cl	4-Cl	(*S*)-$CH(CH_3)_2$	92	**5qq**	69[a]
4rr	5-Cl	4-Cl	(*R*)-$CH(CH_3)_2$	97	**5rr**	48[a]
4ss	5-Cl	4-Cl	(*S*)-CH_2-phenyl	96	**5ss**	40[b]
4tt	5-Cl	4-Cl	(*R*)-CH_2-phenyl	91	**5tt**	40[b]
4uu	5-Cl	4,3-diCl	(*S*)-CH_3	NI	**5uu**	41[c]
4vv	5-Cl	4,3-diCl	(*S*)-$CH(CH_3)_2$	94	**5vv**	66[c]
4ww	5-Cl	4,3-diCl	(*S*)-CH_2-phenyl	94	**5ww**	74[c]

[a] Column chromatography (yields). [b] Chromatotron (yields). [c] Gradient column chromatography. NP: the starting esters were not prepared, thus following reactions were not carried out. NI: not isolated.

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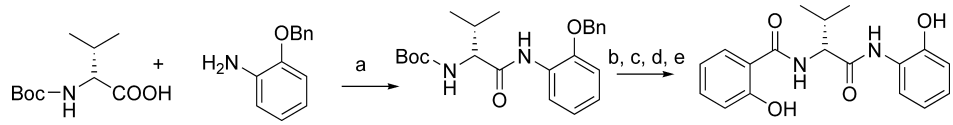
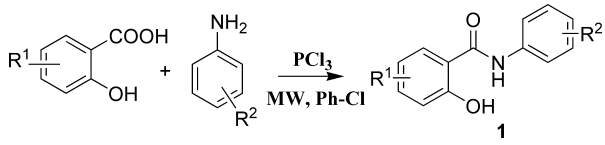
Scheme 1. (*R*)-2-Hydroxy-*N*-[1-(2-hydroxyphenylamino]-3-methyl-1-oxobutan-2-yl)benzamide Synthesis: The Shibasaki Pathway[a]



[a] Reaction conditions: (a) EDC·HCl, HOBt, Et_3N, CH_2Cl_2, 0 °C to rt; (b) 4M HCl/dioxane, 0 °C to rt; (b) *O*-acetylsalicyloyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt; (d) K_2CO_3, $MeOH/CH_2Cl_2$, rt; (e) Pd/C, H_2, $MeOH/CH_2Cl_2$, rt.

Scheme 2. MW Synthesis of SAL **1**



Prepared esters are the starting compounds for our reaction. Their synthesis and possible problems in their preparation were recently published.[3]

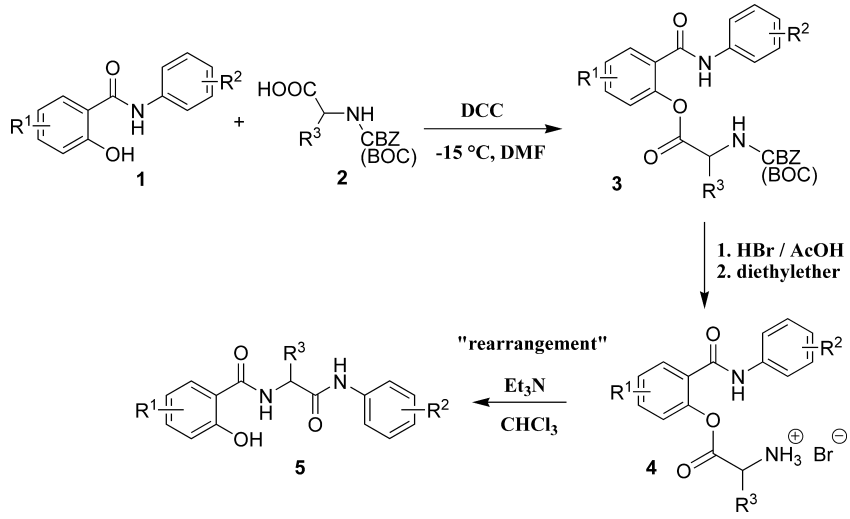
The *N*-deprotection of the amino group failed under generous conditions of hydrogenolysis (H_2/Pd); the ester linkage was found unstable even if different reaction conditions and solvents were used (temperature modification, toluene, ethyl acetate and methanol as solvents). Amino group liberation was finally realized by using 33% solution of hydrogen bromide in glacial acetic acid. Diethyl ether addition precipitated the appropriate hydrobromide salts of SAL-AA esters **4** as white hygroscopic solids in almost quantitative yields, for details see Table 1 and ref 6.

The rearrangement of SAL-AA esters after the amino group deprotection by triethylamine yielded the final products **5**. The proposed mechanism of this rearrangement was recently published.[7] The structure of **5** was unequivocally corroborated by HMBC 2D NMR experiments (Scheme 3).

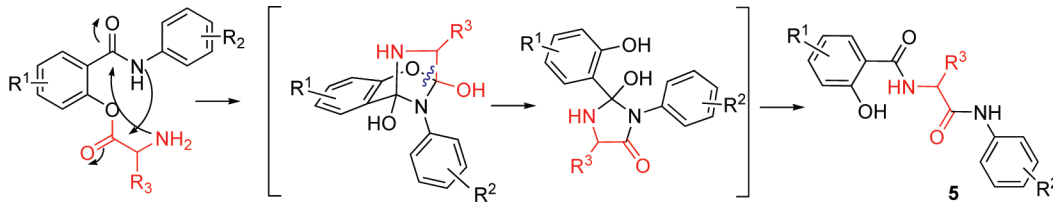
The proposed mechanism of rearrangement is based on the isolation and identification of dehydrated form of reaction intermediate 2-(5-chloro-2-hydroxyphenyl)-1-(3-chlorophenyl)-4-isopropyl-1*H*-imidazol-5(4*H*)-one by 2D NMR and X-ray analysis. The mechanism is carefully described in our recent publication. For further information, see Scheme 4 and ref 7.

This rearrangement has been found general for AA esters **3** and was observed independently on the AA type or electron

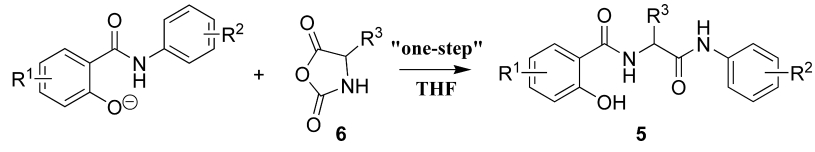
Scheme 3. Synthesis of HBr Salts of *N*-Protected Esters and Their Subsequent Rearrangement



Scheme 4. Proposed Mechanism of Rearrangement[7]



Scheme 5. Leuch Amino Acid Condensation



effects of substituents presented on salicylic/anilide moiety, respectively, as well as the kind of protection of AA amino group.

The same kind of "diamide" **5** was obtained by one step synthesis when Leuch anhydride of amino acid **6** (i.e., Phe, Ala; **5z**, **5dd**) was condensed with potassium or sodium salt of salicylanilides (see Scheme 5).[1] This pathway needs the previous Leuch anhydride of AA preparation.[8]

In conclusion, *N*-deprotection of SAL-AA esters gave a series of original 2-hydroxy-*N*-[1-(2-hydroxyphenylamino)-3-methyl-1-oxobutan-2-yl]benzamides **5** with potential antimycobacterial and antifungal activity.

In contrast to building up the diamide step by step from *N*-Boc amino acid, *O*-protected 2-aminophenol, and *O*-acetylsalicyloyl chloride, here, we are proposing a different method based on the new salicylanilide rearrangement. This approach includes less synthetic steps, as well as wide range of substituents variability on the both benzene rings and alkyl part of the final molecules.

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Supporting Information Available. Experimental procedures and spectroscopic data for prepared compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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(5) (a) Equivalent amount of substituted salicylic acid and aniline were mixed in Ph-Cl. Phosphorus trichloride (0.5 equiv) was added. The mixture was then irradiated in MW reactor MicroSynth (450W) for 20 min to reflux. Then, the reaction mixture was cooled, and the crude product collected by filtration, followed by recrystallization from acetone to obtain pure product. (b) Colombo, M.; Bossolo, S.; Aramini, A. *J. Comb. Chem.* **2009**, *11*, 335–337.

(6) General literature procedure[3b] for compound **3**: *N*-CBZ or *N*-BOC protected 2-amino acid **2** (10 mmol) and substituted salicylanilide **1** (10 mmol) were dissolved in dry DMF (45 mL). The solution was cooled to −15 °C and *N*,*N*′-dicyclohexylcarbodiimide (DCC, 11 mmol) was added in three portions during 1 h. The mixture was stirred for 3 h at the same temperature and stored at +4 °C for 20 h. The precipitate of *N*,*N*′-dicyclohexylurea was removed by filtration, and the solvent was evaporated in vacuo. The crude product **3** was purified by crystallization from ethyl acetate−hexane.

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