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TETRAHEDRON: *ASYMMETRY*

Stereoselective homocoupling of chiral 1-aroylacetyl-2-imidazolidinones by oxidation with Br_2

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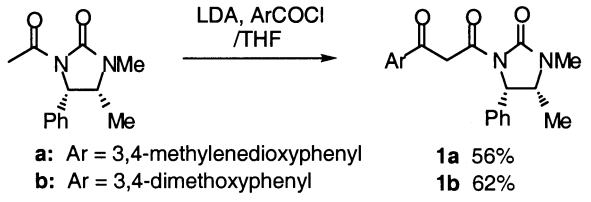
Abstract—The oxidative coupling of sodium enolates of (4*R*,5*S*)-1-aroylacetyl-3,4-dimethyl-5-phenyl-2-imidazolidinones with Br_2 as the oxidant affords the *R*,*R*-dimers stereoselectively. The *R*,*R*-selectivity can be explained by a radical coupling mechanism.

Oxidative homocoupling of β-keto esters has been achieved with I_2[1] or $K_2S_2O_8$[2] as the oxidant. However, the diastereoselectivity of this type of reaction was generally low. On the other hand, we have reported that the oxidative homocoupling of chiral arylacetic acid[3] and 3-arylpropanoic acid derivatives[4] gave optically active dimers stereoselectively. In continuation with these studies, we planned to realize the oxidative homocoupling of chiral aroylacetic acid derivatives, since the optically active dimers formed by such a process are useful precursors for the asymmetric synthesis of furofuran lignans, such as Sesamin[5] and Eudesmin.[6] Herein, we wish to report that the oxidative homocoupling of chiral aroylacetic acid derivatives proceeds stereoselectively when (4*R*,5*S*)-3,4-dimethyl-5-phenyl-2-imidazolidinone is used as a chiral auxiliary and Br_2 is the oxidant.

The starting (4*R*,5*S*)-1-aroylacetyl-3,4-dimethyl-5-phenyl-2-imidazolidinones **1** were prepared by acylation of (4*R*,5*S*)-1-acetyl-3,4-dimethyl-5-phenyl-2-imidazolidinone with aroyl chlorides (Scheme 1). The oxidation of sodium salts of **1** was carried out in THF using several oxidants, such as I_2, Br_2, $CuCl_2$, $CuBr_2$, $TiCl_4$ and $PhI(OAc)_2$. Only Br_2 produced the corresponding dimers **2** in satisfactory yields (Scheme 2). The dimers **2** were obtained as mixtures of two diastereomers. ^1H and ^{13}C NMR spectra clearly showed that the major isomers of **2** were C_2-symmetric (*R*,*R* or *S*,*S*) and the minor ones were C_1-symmetric (*R*,*S*). The major isomers were confirmed to have *R*,*R*-configuration by their conversion to known compounds (vide infra) and *S*,*S*-isomers could not be detected.



Scheme 1.

The reaction of the sodium salts of **1** with bromides **3** (derived from **1** by bromination) also gave the dimers **2** in satisfactory yields (Scheme 3). It is notable that the diastereoselectivities were similar to those in Scheme 2 although the bromides **3** were 6:4 mixtures of two diastereomers. This result suggests that the dimerization proceeds through a radical coupling mechanism.

We next tried mixed-coupling reactions as shown in Scheme 4. The reaction of **1a** (**1b**) with **3b** (**3a**) yields mixed-coupling product **4** together with homocoupling products **2** in substantially statistical ratios. These results also support radical coupling mechanism for this type of reaction.

The results described above suggest that the dimers **2** (**4**) are formed by radical coupling reaction. To explain the *R*,*R*-selectivity, the reaction mechanism illustrated in Scheme 5 can be postulated. Namely, the *anti-Z* type enolate anion **A** generated from **1** with NaH is oxidized to the radical intermediate **B** by Br_2 or bromide **3**,

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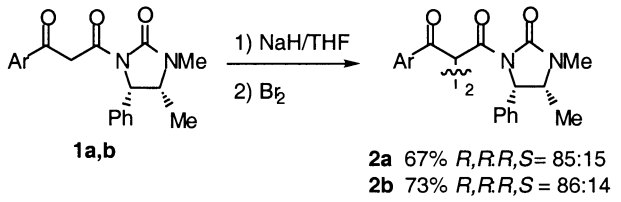
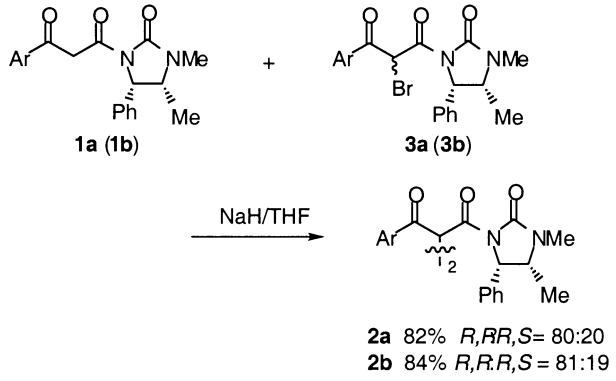
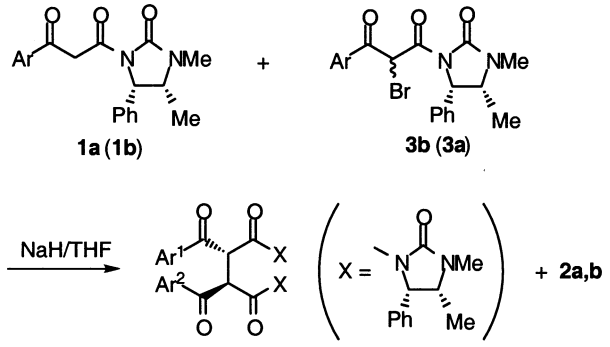


Scheme 2.



Scheme 3.

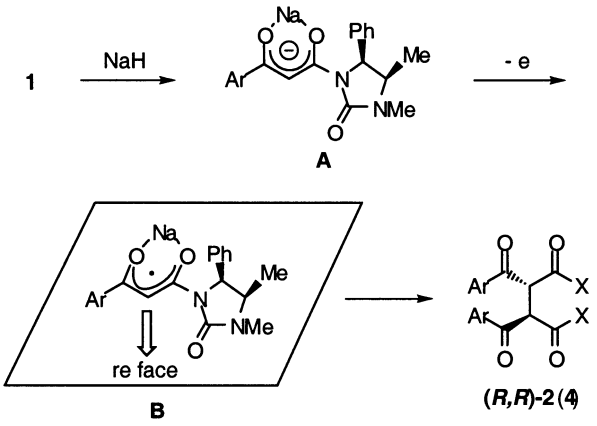


	yield of dimers	(R,R)-4:(R,R)-2a(R,R)-2b
1a + 3b	73%	56 : 22 : 22
1b + 3a	72%	56 : 21 : 23

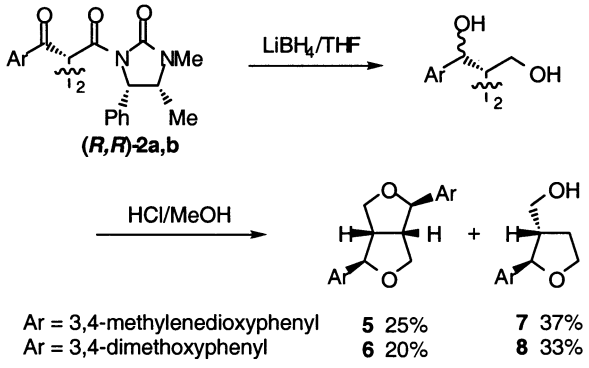
Scheme 4.

which is simultaneously reduced to **B**. The *anti*-Z type radicals **B** couple with each other at the less hindered α side (*Re* face) to give *R*,*R*-isomer of **2** (**4**) stereoselectively. It was confirmed that the dimers **2** (**4**) did not isomerize under the reaction conditions (NaH/THF, rt).

The major isomers of **2a** and **2b** were transformed to (−)-Sesamin **5**[7] and (−)-Eudesmin **6**,[8] respectively, by reduction with $LiBH_4$ in THF and subsequent treatment with HCl in methanol (Scheme 6). Therefore, the *R*,*R*-configuration of the major isomers of **2** was assigned. The yields of **5** and **6** were low probably due to retro-aldol reaction in the reduction step, since tetrahydrofurans **7** and **8** were also formed.



Scheme 5.



Scheme 6.

In summary, the oxidation of (4*R*,5*S*)-1-aroylacetyl-3,4-dimethyl-5-phenyl-2-imidazolidinones with NaH–Br_2 gave the corresponding *R*,*R*-dimers stereoselectively (70–72% de). To our knowledge, this report is the first example of stereoselective dimerization of chiral β-keto acid derivatives. Other chiral auxiliaries for this type of reaction and transformation of the dimers to furofuran lignans are now being investigated.

The general procedure for the oxidative coupling with NaH–Br_2 is as follows: To a suspension of NaH (1.2 mmol) in THF (5 mL) was added a solution of **1** (1.0 mmol) in THF (5 mL) at room temperature under N_2. After the mixture was stirred for 30 min, Br_2 (88 mg, 0.55 mmol) was added. The mixture was stirred for 12 h, diluted with 1M HCl (10 mL), and then extracted with Et_2O. The two isomers of **2** were separated by column chromatography on silica gel (hexane/ethyl acetate). Each isomer of **2** could be further purified by recrystallization from ethyl acetate. All coupling products gave satisfactory spectroscopic data and elemental analyses. (*R*,*R*)-**2a**: mp 244–246°C; $[\alpha]_D^{20}$ −174 (*c* 1.08, $CHCl_3$). (*R*,*S*)-**2a**: mp 226–227°C; $[\alpha]_D^{20}$ +236 (*c* 1.02, $CHCl_3$). (*R*,*R*)-**2b**: mp 228–230°C; $[\alpha]_D^{25}$ −175 (*c* 1.04, $CHCl_3$). (*R*,*S*)-**2b**: mp 145–146°C; $[\alpha]_D^{20}$ +179 (*c* 1.06, $CHCl_3$). (*R*,*R*)-**4**: mp 163–165°C; $[\alpha]_D^{20}$ −142 (*c* 1.05, $CHCl_3$).

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7. (–)-**Sesamin**, **5**: $[\alpha]_D^{22}$ −64.1 (*c* 1.25, $CHCl_3$), lit.[5a] $[\alpha]_D^{22}$ −64.51 (*c* 1.05, $CHCl_3$).
8. (–)-**Eudesmin**, **6**: $[\alpha]_D^{23}$ −63.5 (*c* 1.0, $CHCl_3$), lit.[6b] $[\alpha]_D^{23}$ −64.2 (*c* 1.1, $CHCl_3$).