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Stereoselective Dimerization of α-Keto Amides Using Samarium Diiodide

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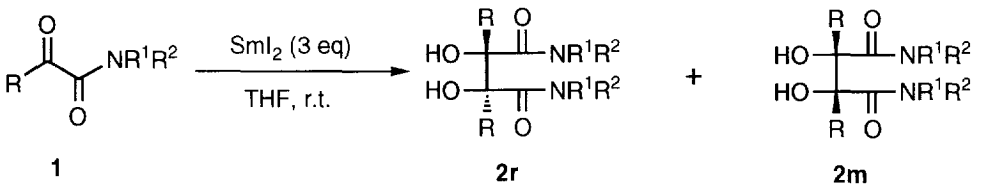
Abstract: α-Keto amides were dimerized in the presence of SmI_2 in THF to give substituted tartaric amides in moderate to good yields. Although the dimerization of the secondary keto amides did not proceed stereoselectively, racemic tartaric amides were produced exclusively in the case of the tertiary keto amides. Copyright © 1996 Elsevier Science Ltd

In view of its easy handling and the wide range of reactivities, samarium diiodide (SmI_2) has become an important one-electron reducing agent since the first applications to synthetic organic chemistry by Kagan and his co-workers in 1977[1] and many reactions of SmI_2 have been reported.[2] On the other hand, there are a few papers regarding the dimerization of α-keto acid derivatives,[3] but these procedures are not satisfactory due to their complexity, low yield, or non-stereoselectivity. Furthermore, there is no report of the dimerization of α-keto amides. In this paper, we describe the reductive dimerization of α-keto amides (**1**) (Scheme 1).



1 **2r** **2m**

Scheme 1

When a solution of *N*-isopropylpyruvamide (**1a**) in THF was slowly added to a suspension of 3 equivalents of SmI_2 in THF at room temperature, a racemic compound (**2ra**) and a meso compound (**2ma**) were obtained in 18% and 37% yields, respectively (Entry 1), and these products could be easily isolated by preparative TLC. The yields of **2ra** and **2ma** could not be improved by changing the reaction conditions. The stereochemistries of **2ra** and **2ma** were determined by X-ray crystal structure analyses.[4] Other secondary pyruvamides (**1b** and **1c**) were subjected to the same reaction conditions as described above, and the corresponding diastereomeric mixtures were obtained (Entries 2 and 3).

Next, we tried the reductive dimerization of tertiary pyruvamides (**1d**, **1e**, and **1f**). Although **1d** gave only *N,N*-diphenyl lactamide in 57% yield (Entry 4), dimerization occurred in the case of **1e** and **1f** (Entries 5 and 6) to give only the racemates (**2rd** and **2re**) in 59% and 94% yield, respectively (*vide infra*). Some *N,N*-diisopropyl α-keto amides (**1g** - **1j**) were similarly dimerized to give the corresponding racemates (**2rf** - **2ri**) in moderate to good yields (Entries 7 - 10). The stereochemistries of **2re**, **2rh**, and **2ri** were determined by X-ray crystal structure analyses[4], and **2rd**, **2rf**, and **2rg** also should be racemates judging from analogous ^{1}H-NMR data.

Investigation of the reaction mechanism of the stereoselective dimerization and its applications is in progress.[5]

Table 1. Reductive Dimerization of α-Keto Amides (**1**)[a]

Entry	Starting Material	R	R^1	R^2	Isolated Yield (%)
1	**1a** :	CH_3-	$(CH_3)_2CH$-	H-	**2ra** : 18[b] , **2ma** : 37[c]
2	**1b** :	CH_3-	Ph-	H-	**2rb** : 41[b,d], **2mb** : 30[c,d]
3	**1c** :	CH_3-	$PhCH_2$-	H-	**2rc** : 25[b,d], **2mc** : 34[c,d]
4	**1d** :	CH_3-	Ph-	Ph-	-[e]
5	**1e** :	CH_3-	$PhCH_2$-	$PhCH_2$-	**2rd** : 59
6	**1f** :	CH_3-	$(CH_3)_2CH$-	$(CH_3)_2CH$-	**2re** : 94
7	**1g** :	CH_3CH_2-	$(CH_3)_2CH$-	$(CH_3)_2CH$-	**2rf** : 90
8	**1h** :	$CH_3CH_2CH_2$-	$(CH_3)_2CH$-	$(CH_3)_2CH$-	**2rg** : 64
9	**1i** :	$PhCH_2CH_2$-	$(CH_3)_2CH$-	$(CH_3)_2CH$-	**2rh** : 56
10	**1j** :	$(CH_3)_3CCH_2CH_2$-	$(CH_3)_2CH$-	$(CH_3)_2CH$-	**2ri** : 83

a) 0.5 mmol of **1** in THF (5 ml) was added slowly to 1.5 mmol of SmI_2 in THF (2 ml). b) More polar compound. c) Less polar compound. d) The stereochemistry was estimated on the basis of ^{1}H-NMR data. e) *N,N*-Diphenyl lactamide was obtained (57%).

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4. **2ra** : $C_{12}H_{24}N_2O_4$; FW 260.33, triclinic, $P\bar{1}$(#2), a = 9.681(1), b = 10.000(1), c = 8.7686(9) Å, α = 103.81(1)°, β = 102.243(9)°, γ = 66.244(8)°, V = 725.9(2) Å^3, Z = 2, D_{calc} = 1.191 g/cm^3, λ(CuKα) = 1.54178 Å, μ = 7.34 cm^{-1}, F(000) = 284, T = 296 K, R = 0.045 for 1986 observations. **2ma** : $C_{12}H_{24}N_2O_4$; FW 260.33, monoclinic, $P2_1/c$(#14), a = 8.6460(6), b = 9.7703(8), c = 9.2555(6) Å, β = 106.786(5)°, V = 748.53(9) Å^3, Z = 2, D_{calc} = 1.155 g/cm^3, λ(CuKα) = 1.54178 Å, μ = 7.12 cm^{-1}, F(000) = 284, T = 296 K, R = 0.051 for 656 observations. **2re** : $C_{18}H_{36}N_2O_4$; FW 344.49, monoclinic, $P2_1/c$(#14), a = 11.953(2), b = 13.432(1), c = 13.459(2) Å, β = 102.243(9)°, V = 2111.7(4) Å^3, Z = 4, D_{calc} = 1.083 g/cm^3, λ(CuKα) = 1.54178 Å, μ = 6.08 cm^{-1}, F(000) = 760, T = 296 K, R = 0.036 for 2106 observations. **2rh** : $C_{32}H_{48}N_2O_4$; FW 524.74, monoclinic, $P2_1/c$(#14), a = 11.590(2), b = 12.439(3), c = 44.677(2) Å, β = 96.446(8)°, V = 6400(1) Å^3, Z = 8, D_{calc} = 1.089 g/cm^3, λ(CuKα) = 1.54178 Å, μ = 5.60 cm^{-1}, F(000) = 2288, T = 296 K, R = 0.042 for 2832 observations. **2ri** : $C_{28}H_{56}N_2O_4$; FW 484.76, trigonal, $R\bar{3}$(#148), a = 35.038(3), c = 13.555(3) Å, V = 14410(3) Å^3, Z = 18, D_{calc} = 1.005 g/cm^3, λ(CuKα) = 1.54178 Å, μ = 5.15 cm^{-1}, F(000) = 4860, T = 296 K, R = 0.050 for 2009 observations. Detailed X-ray crystallographic data of **2ra**, **2ma**, **2re**, **2rh**, and **2ri** are available from the Cambridge Crystallographic Data Centre.
5. The structures of the compounds prepared were confirmed by ^{1}H-NMR, IR, LRMS, and HRMS or elemental analysis.

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