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STEREOCONTROLLED IODOLACTONIZATION OF ACYCLIC OLEFINIC AMIDES

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Abstract: Acyclic olefinic amides were iodolactonized in the mixed solvent of CH_3CN and H_2O (90:10, v/v) under reflux to give products with *trans* configuration of the newly formed iodomethyl to the inherent alkyl group in high yield.

Since iodolactonization is known as a method to prepare synthetically useful γ- and δ-lactones from acyclic carboxylates, their stereospecific transformations have attracted great attentions.[1] Most of the methods lead the mixture of product with *cis* and *trans* configuration of the newly formed iodomethyl to the inherent R^1 or R^2 group.[2,3] During the course of our work for lipase-mediated resolution were needed β-substituted γ-acetyloxymethyl-γ-butyrolactones which derived from direct acetylation of the corresponding γ-iodomethyl-γ-butyrolactones with AgOAc.[4] Thermodynamically controlled iodolactonization from acyclic acids was not good to yield consistent ratios in favor of *trans* isomer over *cis*. Since the separation of *trans* and *cis* isomers is very laborious, a reliable procedure yielding *trans* isomer as a dominant product is required to get *trans*-β-substituted-γ-iodomethyl-γ-butyrolactones. In this report we would like to present a new procedure yielding the thermodynamic products of *trans*-isomers as the

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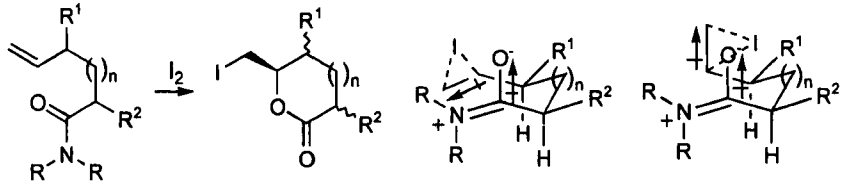
major product from acyclic olefinic amides. Iodolactonization from amides instead of carboxylates has an advantage that no external base is required as a proton scavenger.[3] Therefore we can control the reaction at ease by adjusting only the reaction medium and the temperature.

The starting amides were synthesized either from Meerwein-Eschenmoser variation of the Claisen rearrangement (**1a**, **1d-1e**)[5] or from methylation of *N,N*-dimethylpentenamide (**1f**) and *N,N*-dimethylhexenamide (**1h**).[3a] Others were yielded from amide formation with dialkylamine and the corresponding acids[2b,5b] that prepared either from Claisen rearrangement (**1b** and **1c**) or from the hydrolysis of 5-hexenenitrile (**1g**).



1 **2** **3** **4**

At first we have tried to find the best reaction conditions with the substrate **1a** to lead the *trans*-γ-iodomethyl-β-methyl-γ-butyrolactone. The reaction in THF with H_2O used in common was not quite successful to get *trans* isomer as a major. The *trans:cis* ratio stayed the same varying the content of H_2O (entries 1 and 2). However in the CH_3CN as a solvent the ratio is dependent to the amount of H_2O used. Increasing the content of organic solvent of CH_3CN relative to the H_2O the ratio of *trans* product were much improved from almost 48:52 to 84:16 at the room temperature (entries 3-5). However the reaction rate slowed down. In case of the media of CH_3CN and H_2O (90:10, v/v) the reaction proceeded in less than 10% after 80 h with the ratio of *trans* and *cis* as 84:16 (entry 5). When the reaction temperature was increased to 55°C the reaction was completed in 84 h with the ratio as 79:21 (entry 6). Under reflux the reaction proceeded much faster with better ratio of 91:9 as *trans:cis* (entry 7). This ratio stayed almost same when more CH_3CN was added in the reaction media (entry 8).

These results can be explained by the solvent effect on the dipolar character of the transition states in the conformational equilibrium. Dipole moments generated in the transition state have two different orientations as in eclipse of **3** and in parallel of **4**.[6]

Between two orientations **3** is more favorable with less dipole energy and less steric hindrance compared to **4** in the more polar and protophobic solvent like CH_3CN as a media compared to the less polar and protophilic solvent like THF.[7] However the reaction took a little longer time to complete compared to the reaction in THF due to slow rate of the hydrolysis of amide after cyclization. The reaction did not proceed at all in $CHCl_3$. And the less water content can intrude the reaction better via **3** to yield the thermodynamically favored *trans* product.

Table 1. Iodolactonization of **1a**.

Entry	Solvent	Temp (°C)	Time (h)	*trans:cis* [a,b]
1	THF : H_2O = 95 : 5	rt	4	36 : 65
2	THF : H_2O = 50 : 50	rt	4	38 : 62
3	CH_3CN : H_2O = 50 : 50	rt	14	48 : 52
4	CH_3CN : H_2O = 70 : 50	rt	64	65 : 53
5	CH_3CN : H_2O = 90 : 30	rt	80	84 : 16 [c]
6	CH_3CN : H_2O = 90 : 10	55	84	79 : 21
7	**CH_3CN : H_2O = 90 : 10**	**reflux**	**16**	**91 : 9**
8	CH_3CN : H_2O = 95 : 5	reflux	30	90 : 10

a. The ratio was determined by ^1H NMR.
b. The isolated yields were more than 92% in all entries with one exception of entry 5.
c. The Yield was less than 10%.

Lower ratio was obtained from diethylamide (**1b**) in a little longer reaction time due to the steric hindrance getting toward the reactive conformer in **3** with ethyl on R compared to the same conformer with methyl on R. Under this condition diisopropylamide (**1c**) was inert. Driving the *trans* isomers also succeeded from all the other starting dimethylamides (**1d** and **1e**) with β-substituents of Et and Ph with the ratio of 94:6 and 96:4 respectively. When the substituent got bigger the longer reaction time required. Thermodynamic product formation of δ-lactone was also achieved with the ratio of 73:27 from **1g**. 1,3-Asymmetrical induction from 2-methyl-4-pentenamide (**1f**) or 2-methyl-5-hexenamide (**1h**) was poor compared to the 1,2-asymmetrical induction as the ratio of 62:38 and 71:29, respectively. Relatively low ratios from **1f**, **1g** and **1h** may arise from the conformational freedom to reduce the transition state energy difference between **3** and **4**.

Table 2. Iodolactonization of **1**.

Amide	n	R^1	R^2	R	Time (h)	Yield (%)	*trans:cis* [a,b]
1a	0	Me	H	Me	16	98	91 : 9
1b	0	Me	H	Et	18	85	75 : 25
1c	0	Me	H	*i*-Pr		no rxn	
1d	0	Et	H	Me	38	89	94 : 6
1e	0	Ph	H	Me	54	97	96 : 4
1f	0	H	Me	Me	84	90	62 : 38
1g	1	Me	H	Me	2	93	73 : 27
1h	1	H	Me	Me	3	85	71 : 29

a. The ratio was determined by ^{1}H NMR.
b. The ratio was an average of three runs.

In conclusion we could iodolactonize acyclic olefinic amides to the thermodynamically favored *trans* isomers (**2a, 2d** and **2e**) with the best ratios, so far as we know[2a], in the mixed solvent of CH_3CN and H_2O (90:10, v/v) under reflux in high yield.

Preparation of the starting amides: The starting amides of **1a, 1d** and **1e** were synthesized following the known procedure[5] of Meerwein-Eschenmoser variation of the Claisen rearrangement. The other amides **1b, 1c** and **1g** were yielded from the corresponding acids[2a,b] with dialkylamine. *N,N*-Dimethyl-2-methyl-4-pentenamide (**1f**) and *N,N*-dimethyl-2-methyl-5-hexenamide (**1h**) were known.[3a]

***N,N*-Dimethyl-3-methyl-4-pentenamide (1a):** ^{1}H NMR δ 0.95 (d, 3H, J = 6.8 Hz), 2.13 (dd, 1H, J = 14.9, 7.6 Hz), 2.27 (dd, 1H, J = 15.0, 6.6 Hz), 2.56 – 2.74 (m, 1H), 2.83 (s, 3H), 2.90 (s, 3H), 4.79 – 4.96 (m, 2H), 5.72 (ddd, 1H, J = 17.4, 10.3, 6.8 Hz); ^{13}C NMR δ 19.3, 33.9, 35.0, 37.1, 39.6, 112.5, 143.1, 171.6.

***N,N*-Diethyl-3-methyl-4-pentenamide (1b):** ^{1}H NMR δ 1.02 (d, 3H, J = 6.8 Hz), 1.13 (m, 6H), 2.24 (m, 2H), 2.54 – 2.71 (m, 1H), 3.29 (m, 4H), 4.88 – 5.03 (m, 2H), 5.79 (ddd, 1H, J = 17.2, 10.2, 6.8 Hz); ^{13}C NMR δ 12.9, 14.3, 19.3, 34.2, 39.5, 40.0, 41.9, 112.7, 143.3, 170.9.

***N,N*-Di-*i*-propylyl-3-methyl-4-pentenamide (1c):** ^{1}H NMR δ 1.02 (d, 3H, J = 6.8 Hz), 1.16 (d, 6H, J = 6.6 Hz), 1.34 (d, 6H, J = 6.2 Hz), 2.10 – 2.35 (m, 2H), 2.70 (sept, 1H, J = 6.8 Hz), 3.44 – 3.49 (m, 1H), 3.95 (sept, 1H, J = 6.6 Hz), 4.93 (s, 1H), 4.98 (d, 1H, J = 6.4 Hz), 5.70 – 5.88 (m, 1H); ^{13}C NMR δ 19.4, 20.5, 20.9, 34.2, 41.7, 45.5, 48.3, 112.5, 143.5, 170.7.

***N,N*-dimethyl-3-ethyl-4-pentenamide (1d):** ^{1}H NMR δ 0.85 (t, 3H, J = 7.2 Hz), 1.17 – 1.54 (m, 2H), 2.28 (d, 2H, J = 12.2 Hz), 2.54 – 2.67 (m, 1H), 2.91 (s, 3H), 2.98 (s, 3H), 4.90 – 5.10 (m, 2H), 5.62 (dq, 1H, J = 8.0, 10.2 Hz); ^{13}C NMR δ 11.4, 27.2, 35.3, 37.4, 38.3, 41.9, 114.7, 141.5, 172.1.

***N,N*-dimethyl-3-phenyl-4-pentenamide (1e):** ^{1}H NMR δ 2.54 – 2.67 (m, 2H), 2.77 (s, 3H), 2.79 (s, 3H), 3.92 (q, 1H, J = 7.0 Hz), 4.94 (dd, 1H, J = 9.4, 1.4 Hz), 5.02 (d, 1H, J = 1.4 Hz), 5.90 – 6.07 (m, 1H), 7.08 – 7.27 (m, 5H); ^{13}C NMR δ 34.8, 36.7, 38.3, 45.0, 114.0, 126.1 127.3, 128.1, 140.5, 142.9, 170.8.

***N,N*-dimethyl-4-methyl-5-hexenamide (1g):** ^{1}H NMR δ 0.94 (d, 3H, J = 6.8 Hz), 1.42 – 1.70 (m, 2H), 2.00 – 2.15 (m, 1H), 2.25 (t, 2H, J = 6.8 Hz), 2.86 (s, 3H), 2.92 (s, 3H), 4.86 – 4.97 (m, 2H), 5.61 (ddd, 1H, J = 17.4, 10.3, 6.8); ^{13}C NMR δ 20.1, 30.8, 31.4, 35.1, 37.0, 37.5, 113.2, 143.9, 173.1.

General Procedure for Iodolactonizations: To a stirred solution of *N,N*-dimethyl-3-methyl-4-pentenamide (**1a**) (1.0 g, 7.9 mmol) in CH_3CN and H_2O (22 ml / 2 ml) under nitrogen atmosphere in dark was added iodine (2.7 g, 10.6 mmol) and the resulting solution was refluxed until all starting material was consumed on TLC. The reaction mixture was poured into brine. The reaction product was extracted with EtOAc (3 x 30 ml). Organic layer was washed successively with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction product was purified by flash chromatography with the eluent of *n*-hexane and EtOAc (5:1, v/v) to give *trans*-γ-iodomethyl-β-methyl-γ-butyrolactone (**2a**) with the removal of minor *cis* isomer. All of the iodolactonized products (**2a**^{2b}, **2e**^{2b}, **2f**^{2a}, **2g**^{2a} and **2h**^{2a}) were known except **2d**.

***trans*-γ-Iodomethyl-β-ethyl-γ-butyrolactone (2d):** ^{1}H NMR δ 0.94 (t, 3H, J = 7.2 Hz), 1.33-1.70 (m, 2H), 2.14-2.33 (m, 2H), 2.79 (dd, 1H, J = 19.8, 11.2 Hz), 3.31 (dd, 1H, J = 10.8, 4.8 Hz), 3.41 (dd, 1H, J = 10.8, 5.4 Hz), 4.10 (dd, 1H, J = 10.2, 5.0 HZ); ^{13}C NMR δ 7.08, 11.3, 26.2, 34.3, 42.1, 82.9, 175.5. Anal. Calcd for $C_7H_{11}O_2I$: C, 33.1; H, 4.36. Found: C, 33.2; H, 4.57.

Acknowledgments

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