Pergamon

Tetrahedron Letters, Vol. 35, No. 42, pp. 7711-7714, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01638-0

Stereoselective Reaction of a Chiral Assisted Amide Enolate Ion with 1-Iodonaphthalene by the $S_{RN}1$ Mechanism

Guillermo A. Lotz,[1a] Sara M. Palacios,[1a]* Roberto A. Rossi[1b]*

Centro de Química Aplicada and Departamento de Química Orgánica, Facultad de Ciencias Químicas,
Universidad Nacional de Córdoba, Suc. 16, CC 61, 5016 Córdoba, Argentina.

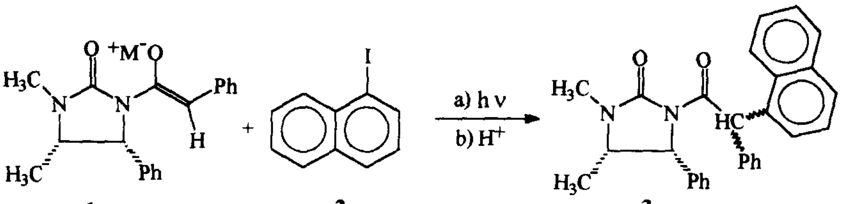
Abstract: *The photostimulated reaction of the chiral assisted amide enolate ion 1 with 1-iodonaphtalene 2 gave the isomeric substitution products 3 with diastereomeric excess depending of the counter ion.* Li^+ *(at -78°C) and Ti(IV) were found to be the most effective (the diastereomeric ratio > 99). These reactions were done in liquid ammonia and are suspected to follow the* $S_{RN}1$ *mechanism.*

In the last few years, addition of radicals to the double bond by chain processes has been extensively studied especially in the intramolecular cyclization[2a] and the intermolecular reactions.[2b] Both types of reaction presented high stereoselectivity when the radical or the unsaturated moiety presented chirality.[3]

The mechanism of the radical nucleophilic substitution ($S_{RN}1$) is a radical chain process that allows to substitute aromatic and aliphatic halides through radical intermediates. Among the different functionalizations that could be accomplished, the introduction of an aromatic moiety to an enolate ion seems to be the most attractive.[4] The reaction shows exclusively C-substitution,[4] and the coupling rate constant between aryl radicals and enolate ions has been determined to be as high as $4.2\ 10^{10} M^{-1}\ s^{-1}$.[5] It remains to be shown if radicals react stereoselectively to a carbanion nucleophile attached to a chiral auxiliary.

We now demonstrate for the first time that naphthyl radicals can react stereoselectively with chiral assisted amide enolate ions by the $S_{RN}1$ mechanism of nucleophilic substitution.

The photostimulated reaction[6] of the amide enolate ion **1a** and 1-iodonaphthalene (**2**) in liquid ammonia afforded the diastereomeric isomers **3** (eq.1).[7] The reaction of **1a** with **2** in dark conditions did not yield substitution products.



1 **2** **3** (1)

1a: M$^+$ =Li$^+$; **1b**: M$^+$=Na$^+$; **1c**: M$^+$=K$^+$; **1d**: M$^+$ =Cs$^+$; **1e**: M$^+$=Ti(IV)

The reaction has a high dependence on the metal counter ion. The reaction was followed by HPLC,[8] where the diastereomers separated with a 2 min retention time difference. All the ions studied presented selection, but the highest was reached with Li$^+$ at low temperature (-78°C) and with Ti(IV).

When the nucleophile was lithium amide enolate ion **1a**,[9] the diastereomeric ratio (DR) of substitution product was 8.2:1 (Expt. 1, Table I), while with **1b** with sodium as counter ion, the DR was 2.2:1 (Expts. 6-7, Table I), similar to potassium enolate ion (**1c**) where the DR obtained was 1.8:1. When cesium sulfate was added to a solution of **1c**, no major change in the selection is observed (Expt. 9, Table I).

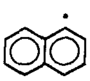
As an estimation to see if the cation exchange is effective, we prepared the potassium enolate **1c** and LiCl was added to the reaction observing a better selection (DR=2.9:1) than with **1c** itself. However the addition of 1 equivalent of $TiCl_4$ to the solution of **1c**, and after the corresponding photostimulated reaction with **2**, the HPLC run showed only the most abundant isomer (Expt. 10, Table I).

High selectivity was also observed in the reaction of **1a** with **2** at lower temperature (-78 °C) yielding only one diastereomer as far as the HPLC detention range (detectable up to a DR = 99:1).

These reactions are suspected to follow the $S_{RN}1$ nucleophilic substitution process, where nucleophile **1** transfers an electron to substrate **2** stimulated by light (eq. 2). The radical anion $\mathbf{2}^{\cdot-}$ thus formed fragments to give the radical **4** and iodide ions (eq. 3); the radical intermediate **4** reacts with the amide enolate ion **1** to give the radical anion $\mathbf{3}^{\cdot-}$ (eq. 4), which by electron transfer to the substrate **2** gives both isomeric substitution products **3** and the radical anion $\mathbf{2}^{\cdot-}$ (eq. 5), which continues the chain process.

$$\mathbf{1} + \mathbf{2} \longrightarrow \mathbf{2}^{\cdot-} \qquad (2)$$

$$\mathbf{2}^{\cdot-} \longrightarrow$$



$$+ \ I^- \qquad (3)$$

4

$$\mathbf{4} + \mathbf{1} \longrightarrow \mathbf{3}^{\cdot-} \qquad (4)$$

$$\mathbf{3}^{\cdot-} + \mathbf{2} \longrightarrow \mathbf{2}^{\cdot-} + \mathbf{3} \qquad (5)$$

In the coupling reaction between radical **4** and **1** (eq. 4) the selection occurs, and we think that it occurs by a preferential approximation through one face of the planar enolate double bond due to the steric hindrance of the imidazolidyl-2-one group which has a certain stereoisomeric disposition.

The remarkable selectivity by the titanium and lithium amides could be explained in terms of better complexation capacity of the Ti(IV) and Li^+, which by coordination of both carbonyl groups avoids the rotation of N-CO bond and the subsequent formation of the other conformer.

The absolute configuration is under determination and will be reported elsewhere.

In conclusion, enolate ions attached to a chiral auxiliary such as nucleophile **1** can react stereoselectively with aryl radicals by the $S_{RN}1$ mechanism with high diastereomeric excess. This reaction open an interesting route to chiral diarylacetic acids. Work is in progress with other chiral auxiliaries and other carbanions.

TABLE I: Photostimulated Reaction of **1a-d** with **2** in Liquid Ammonia.[a]

Expt.	**M^+**	**Substitution Products 3 Yields (%)[b]**	**Diastereomeric Ratio (DR)**
1	Li	52	8.2
2	Li	90	6.1
3[c]	Li	57	>99
4[d]	Li	-	-
5[e]	Li	37	2.9
6	Na	44	2.2
7	Na	Not quantified	2.1
8	K	28	1.8
9[e]	Cs	62	1.7
10[e]	Ti(IV)	43	>99

[a] The reaction were done in refluxing liquid ammonia (-33 °C), unless otherwise indicated (**1** in 4.6×10^{-3} M, **2** in 2.3×10^{-3} M). The quantifications were carried out by HPLC. [b] Yields relative to **2**. [c] The reaction temperature was -78 °C. [d] Dark reaction. [e] 1 equivalent of a salt of the indicated ion was added to the **1c** enolate ion solution.

Acknowledgments: G.A.L. gratefully acknowledges receipt of a fellowship from the Universidad Nacional de Córdoba. This work was partially supported by CONICOR, CONICET and the International Foundation for Science (Grant F/1378/2).

References and Notes

1. (a) Centro de Química Aplicada. (b) Departamento de Química Orgánica.
2. (a) Beckwith A. L. J.; Ingold, K. U. *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, **1980**, vol 1, p. 162. (b) Giese B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon, Oxford, **1986**.
3. (a) Beckwith, A. L. J.; Schiesse, C. H. *Tetrahedron* **1985**, *41*, 3925. (b) Giese, B. *Angew. Chem. Int. Eng. Ed.* **1988**, *28*, 969. (c) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296.
4. For Reviews, see: (a) Norris, R. K. *The Chemistry of Functional Groups*; Patai, S., Rappoport, Z., Eds.; Wiley; Chichester, UK, **1983**; Suppl. D, Chapter 16. (b) Rossi, R.A.; de Rossi R.H. *Aromatic Substitution by the $S_{RN}1$ Mechanism*, ACS Monograph 178, Washington, D.C. **1983**. (c) Norris, R. K. *Comprehensive Organic Synthesis*, Trost, B. M., Ed., Vol. 4, Pergamon, **1991**.
5. This value corresponds to the coupling reaction of 1-naphthyl radical with acetone enolate ion in liquid ammonia. Saveant, J. M. *Bull. Soc. Chim. France*, **1988**, 225.
6. Irradiation was conducted in a reactor equipped with two 250-W lamps emitting maximally at 350 nm (Philips Model HPT, air refrigerated).
7. The structures of both isomers of products **3** were confirmed by ^{1}H and ^{13}C NMR (200 MHz). Ordering information is given on any current masthead page. Anal. Calcd. for $C_{29}H_{26}N_2O_2$: C:80.18; H: 5.99; N: 6.45. Found for the most abundant isomer: C: 80.74; H: 6.09; N: 6.50. Found for the other isomer C: 80.16; H: 6.16; N: 6.40.
8. The HPLC runs were done in a C18 column and ACN/Water (gradient from 60:40 to 65:35 in 40 min.) as eluent.
9. The nucleophile was prepared *in situ* following previous procedures. See Palacios, S. M.; Asís, S. E.; Rossi, R. A. *Bull. Chem. Soc. France* **1993**, *130*, 111.

(*Received in USA* 14 *June* 1994; *revised* 22 *August* 1994; *accepted* 23 *August* 1994)