LITHIUM IODIDE-CATALYZED CONJUGATE ADDITION OF β -DICARBONYL COMPOUNDS

R. Antonioletti,^{a)} F. Bonadies,^{a)} E. S. Monteagudo,^{b)} A. Scettri,^{a)*}

^{a)}Centro CNR di Studio per la Chimica delle Sostanze Organiche Naturali, Dipartimento di Chimica, Università "La Sapienza", P.le A. Moro 5, 00185 Roma, Italy. ^{b)}Departamento de Quimica Organica, Facultad de Ciencias Exactas y Naturales, Ciudad Universitaria, Buenos Aires, Argentina.

Abstract: Lithium iodide proves to be a very efficient catalyst for Michael addition of β -dicarbonyl compounds. The successful application of this methodology to $\alpha\beta$ -unsaturated aldehydes allows an improved approach to 5.6-disubstituted cvclohex-2-en-1-ones.

The Michael reaction is widely employed in organic synthesis for effecting C-C bond formation. in particular, many procedures, based on the conjugate addition of β -dicarbonyl compounds under neutral conditions, have been proposed in these last years,¹⁻⁴ since the conventional base-catalyzed processes are affected by undesired side-reactions such as auto-condensations, bis-additions, polymerizations.⁵ Neverthe the case of $\alpha\beta$ -unsaturated aldehydes the above problems have been only partially circumvented by phase-transfer catalysis.⁶

In the course of investigations on the reactivity of active methylene compounds, we have found that lithium iodide is a very efficient catalyst for the conjugate addition of β -diesters, β -ketoesters, linear and cyclic β -diketones. In fact, as reported in table for the representative Michael acceptor 2, in the presence of catalytic amounts of lithium iodide (1-5 %) in refluxing dimethoxyethane (DME), the formation of adducts 3 takes place with excellent yields.



Entry	R ¹	R ²	R ³	Reac.time(h)	Catal.(%mol)	Yield(%) ^a
a	Me	OEt	Н	24	1	90 È É
b	Me	Me	н	36	1	94
с	Ph	OEt	н	24	1	9 1
d	OEt	OEt	н	48.	5	92
e	Me	OEt	Et	12 ^b	2	82
f	(CH2)4		Н	20	1	80

Table - LiI-catalyzed Michael addition of β -dicarbonyl compounds.

^{a)}All the yields refer to isolated, chromatographically pure compounds. All the assigned structures have been confirmed by spectroscopic data (IR, ¹H-NMR, MS).^{7 b)}In this case the reaction has been carried out in refluxing dioxane.

As regards the field of applicability of the above procedure, it has to be noted that β -substituted $\alpha\beta$ -unsaturated ketones (for ex. cyclohex-2- en-1-one 2b) undergo the usual addition with satisfactory rate in the presence of increased amounts of LiI (10% mol) with formation in efficient way of the adducts of type 4, as 1:1 mixture of diastereoisomers. On the contrary, $\beta\beta$ -disubstituted $\alpha\beta$ -unsaturated ketones (for ex 2c) have proven to be non-reactive under a wide variety of experimental conditions.



Furthermore, more interestingly, we have found that the same procedure can be successfully extended to $\alpha\beta$ -unsaturated aldehydes and this result has been conveniently exploited for the achievement of an improved, one-pot methodology of synthesis of 5,6-disubstituted cyclohex-2-en-1-ones of type 6, known key-intermediates in the synthesis of natural products.^{8,9} In fact, crude adducts 5, submitted to the action of an acid ion exchanger without any previous isolation and purification, are smoothly converted into 6 by intramolecular aldol condensation.



In a typical experimental procedure a solution of 1 (3 mmol), crotonaldehyde (3.6 mmol) and lithium iodide (0.15 mmol) in dimethoxyethane (5 ml) is stirred at reflux till disappearance of starting materials. Then Amberlyst H-15 (1 g) is added to the crude mixture and stirring is prolonged for 16 h. After the usual work-up, purification by silica gel column chromatography affords cyclohexenones 6.10

REFERENCES

- 1) K. Watanabe, K. Miyazu, K. Irie, Bull. Chem. Soc. Jpn., 1982, 55, 3212.
- 2) J. Boyer, R. J. P. Corrin, R. Perz, C. Réyé, J. Chem. Commun., 1981, 122.
- 3) J. M. Nelson, P. N. Howell, G. C. De Lullo, G. L. Landen, R. A. Henry, J. Org. Chem., 1980, 45, 1246.
- 4) A. Corsico Coda, G. Desimoni, P. Righetti, G. Tacconi, Gazz. Chim. Ital., 1984, 114, 417.
- 5) E. Bergmann, D. Ginsburg, R. Pappo, Org. React., 1959, 10, 179-557.
- 6) G. V. Kryshtal, V. V. Kulganek, V. F. Kucherov, L. A. Yanovskaya, Synthesis, 1979, 107.
- 7) For ex. ethyl 2-acethyl-5-oxo-hexanoate (entry a); IR (1%, CCl4): 1745, 1720 cm¹. ¹H-NMR (CDCl₃): δ 4.17 (q, 2H; J = 7 Hz), 3.46 (t, 1H; J = 7 Hz), 2.47 (t, 2H; J = 7Hz), 2.21 (s, 3H), 2.2-2.0 (m, 2H), 2.08 (s, 3H), 1.23 (t, 3H; J = 7 Hz). Ms (m/z): 200 (M⁺).
- 8) F. M. Hauser, S. A. Pogany, Synthesis, 1980, 814.
- 9) A. Gerhard, R. Muntwyler, W. Keller- Schierlein, Helv. Chim. Acta, 1975, 58, 1323.
- 10) On the ground of ¹H-NMR data products 6 are obtained as 9:1 mixture of trans-cis stereoisomers.

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