

ULTRASOUND IN ORGANIC SYNTHESIS 15¹. RADICAL CYCLISATION
 OF O-ALLYL BENZAMIDES VIA THE SONOCHEMICALLY GENERATED RADICAL ANIONS

Jacques Einhorn, Cathy Einhorn and Jean-Louis Luche*

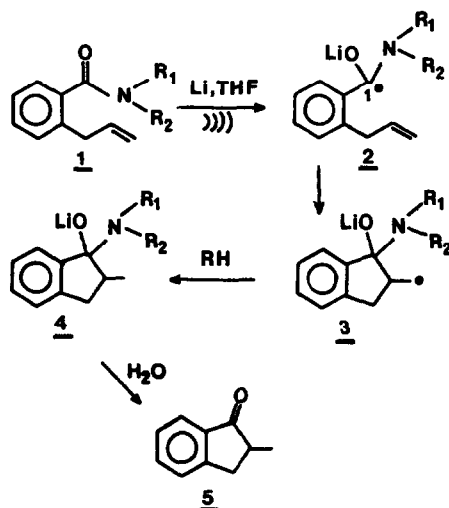
Laboratoire d'Etudes Dynamiques et Structurales de la Sélectivité,
 Université Joseph FOURIER (Grenoble I)
 BP.68, 38402 Saint Martin d'Hères, France

Abstract : By reaction with lithium metal in THF under sonochemical activation, o-allyl tertiary benzamides are easily cyclised to 2-methyl-indanone. Yields strongly depend on the substitution pattern of the nitrogen atom.

Synthetic methods based on carbon-carbon bond formation by radical pathways are of increasing importance in organic chemistry². In the most general case, free radical chain processes are involved, requiring a catalytic initiation step. The less common reactions involving radical anions have been studied e.g. in the case of ketyl radical anions produced by electroreduction³, dissolving metal reduction⁴⁻⁶ or photochemically induced electron transfer⁷. While trying to extend Bouveault type sonochemical reactions, we noticed that delocalised radical anions are very efficiently formed from tertiary benzamides and alkali metals in etheral solvents, under ultrasound activation. Such species which have already been prepared by electroreduction and studied by EPR⁸ appear to be valuable synthetic intermediates and we describe now a new radical cyclisation of o-allyl benzamides, summarized in the following scheme.

Table			
Entry	$\begin{matrix} R^1 \\ \\ N \\ \\ R^2 \end{matrix}$	Sonication time (min) ^a	yield of <u>5</u> ^b %
1	$N(CH_3)_2$	10	25
2	$N(C_2H_5)_2$	15	34
3	$N(i-C_3H_7)_2$	15	60.
4	$N(CH_3)(t-C_4H_9)$	10	95(84) ^c

^a Given for optimal yields. ^b Determined by GC with n-tetradecane as standard. ^c Isolated yield in parentheses.



The results shown in the table indicate that the yield of 2-methyl indanone 5 depends highly on the nature of the substituents R¹ and R² on the nitrogen atom, as it increases along the

sequence $R^1=R^2=CH_3$, $R^1=R^2=C_2H_5$, $R^1=R^2=iC_3H_7$. This observation, in a first approach, seems to be correlated with the spin density on the primarily formed radical anion 2 (scheme). Analogously, spin densities at C-1 on the ortho unsubstituted benzamides, determined by EPR studies⁸ of the delocalized radical anions follow the same sequence.

Steric crowding, which increases in the same order, becomes unfavorable to cyclisation only in the case of very congested amides as 2,2,6,6-tetramethyl-piperidide and no methyl-indanone is obtained. An optimum substitution is reached with $R^1=tC_4H_9$, $R^2=CH_3$ (table) which gives an excellent yield of 5. Other substituents ($R^1=CH_3$, $R^2=C_6H_5$, $CH_2C_6H_5$) are much less effective.

Few other products of low molecular weight are formed in this reaction : traces of o-allyl benzaldehyde and minor amounts of 1-tetralone formed by 6-endo trig⁹ radical cyclisation. 1-Naphthol may also be present, especially for $R^1R^2=(CH_2)_4$ (yield up to 90%). It should result from an ionic reaction pathway as recently described by Snieckus et al¹⁰. Besides these identified by-products, variable amounts of highly polar polymeric material are formed in each case, corresponding to the material balance.

The reaction is carried out in a common laboratory ultrasonic cleaner or, preferably, in the reactor described previously¹¹, using 1 mmole of o-allyl amide, in 30 ml of anhydrous THF under argon, and excess lithium, at $-20^\circ C$. The reaction was monitored by GC (SE 30 column, 10% on Chromosorb) and TLC. The mixture is hydrolysed (aq. NH_4Cl) and worked up as usual. Without ultrasound the reaction starts after erratic induction periods and proceeds slowly, giving very poor yields of cyclisation products and larger amounts of oligomeric material.

The chemical evolution of radical anions derived from aldehydes, ketones and esters has been the subject of many studies¹², but only a few studies with no synthetic applications have been developed in the case of amides.

The cyclisation reaction described here may offer, coupled with ortho allylation of benzamides¹³, a fast and regiospecific access to 1-indanones, some of them being of biological interest¹⁴. The scope and limitations of this reaction such as the possible extensions to other types of radical anions are currently under study.

Acknowledgements : The authors thank Dr. A.E. Greene for fruitful discussions. Financial support from the CNRS is gratefully acknowledged.

REFERENCES AND FOOTNOTES

1. Previous paper : EINHORN, C. ; ALLAVENA, C. ; LUCHE, J.L. *Chem. Commun.* 1988 in press.
2. GIESE, B. "Radicals in Organic Synthesis : Formation of Carbon-Carbon Bonds" Pergamon Press, Oxford, 1986.
3. PATTENDEN, G. ; ROBERTSON, G.M. *Tetrahedron* **41**, 4001 (1985) and ref. cited.
4. PRADHAN, S.K. ; KADAM, S.R. ; KOHLE, J.N. ; RADHAKRISHNAN, T.V. ; SOHANI, S.V. ; THAKER, V.B. *J. Org. Chem.* **46**, 2622 (1981) and ref. cited.
5. IKEDA, T. ; HUTCHINSON, C.R. *J. Org. Chem.* **50**, 5193 (1985).
6. COREY, E.J. ; PYNE, S.G. *Tetrahedron Lett.* **24**, 2821 (1983).
7. BELOTTI, D. ; COSSY, J. ; PETE, J.P. ; PORTELLA, C. *Tetrahedron Lett.* **26**, 4591 (1985).
8. KLAGES, C.P. ; VOSS, J. *Chem. Ber.* **113**, 2255 (1980).
9. BALDWIN, J.E. *Chem. Commun.* 734 (1976).
10. SIBI, M.P. ; DANKWARDT, J.W. ; SNIIECKUS, V. *J. Org. Chem.* **51**, 271 (1986).
11. LUCHE, J.L. ; PETRIER, C. ; DUPUY, C. *Tetrahedron Lett.* **25**, 3463 (1984).
12. MARCH, J. "Advanced Organic Chemistry", 3rd Ed, J. Wiley, New York, 1985 p1110-1112 and 1113-1116.
13. SIBI, M.P. ; TALILMIAH, M.A. ; SNIIECKUS, V. *J. Org. Chem.* **49**, 737 (1984).
14. CRAGOE, E.J. ; GOULD, N.P. ; WOLTERS DORF, O.W. ; ZIEGLER, C. ; BOURKE, R.S. ; NELSON, L.R. ; KIMELBERG, H.J. ; WALDMAN, J.B. ; POPP, A.J. ; SEDRANSK, N. *J. Med. Chem.* **25**, 567 (1982).