Tetrahedron Letters, Vol. 34, No. 3, pp. 517-520, 1993
Printed in Great Britain

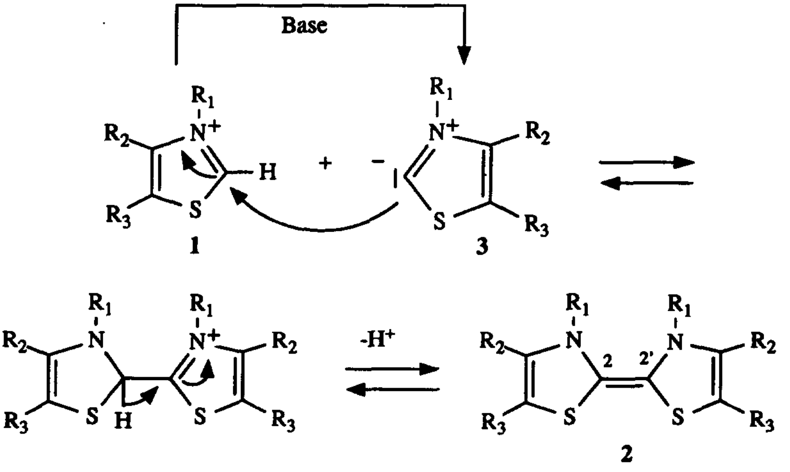
0040-4039/93 $5.00 + .00
Pergamon Press Ltd

New Evidence Supporting Bis(thiazolin-2-ylidene)s as the Actual Catalytic Species in the Benzoin Condensation.

Josep Castells, Laura Domingo, Francisco López-Calahorra*, and Josep Martí
Departament de Química Orgànica, Universitat de Barcelona, Martí i Franquès, 1-11, 08028 Barcelona, Spain.

Abstract: Polymethylene-bridged (n= 2-8) thiazolium and benzothiazolium salts (plus bases) are used as catalysts for the benzoin condensation and it is found that catalytic activity depends strongly on the methylene bridge length. This result supports a previous postulation that bis(thiazolin-2-ylidene)s, and not thiazolin-2-ylidenes, are the catalytic species in the benzoin condensation catalyzed by thiazolium salts plus base.

The benzoin condensation can be catalyzed by cyanide ion,[1-3] thiazolium salts **1** plus bases,[4,5] or bis(thiazolin-2-ylidene)s **2**[6,7]. Deprotonation of thiazolium ions affords thiazolin-2-ylidenes **3** which, according to the classical proposal of Breslow,[8] would be the actual catalytic species in the benzoin condensation and related reactions. However, when adding a base to a solution of thiazolium salt, bis(thiazolin-2-ylidene)s **2** must be formed *in situ* by nucleophilic attack of the nascent thiazolin-2-ylidenes **3** on the surrounding thiazolium ions[9-12] (Scheme), as recently shown by Jordan and Chen using NMR spectroscopy[13].



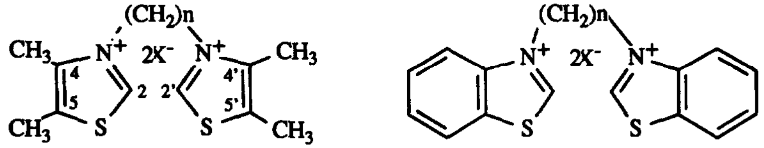
Scheme

Surprisingly, the above nucleophilic carbene chemistry[14-16] is frequently ignored in the benzoin condensation and related fields, including the biochemical ones in which thiamine pyrophosphate acts as the coenzyme[17,18]. In a previous paper we have demonstrated the complete lack of catalytic activity of thiazolin-2-ylidenes generated by desilylation of 2-(trimethylsilyl)thiazolium[19], that is to say, under conditions where formation of bis(thiazolin-2-ylidene)s is impossible, and as a consequence of these works we have postulated what bis(thiazolin-2-ylidene)s are the only catalytic species in the benzoin condensation.

In support of our views, we report here that *the catalytic activity of 3,3'-polymethylene-bridged thiazolium and benzothiazolium salts depends strongly on the methylene bridge length.*

Preparation of 3,3'-polymethylene-bridged thiazolium salts and their use as catalysts in the benzoin condensation.

These molecules[20] were obtained using α,ω-dibromoalkanes as the quaternizing agents in refluxing acetonitrile and an excess of thiazole to favour the desired double quaternization. Two series of bridged thiazolium bromides were prepared in this way, one starting from 4,5-dimethylthiazole (series 4) (Figure) and the other from benzothiazole (series 5); for each series, the length of the bridge covered the range from n=3 to n=8 methylene units. Attempts to use 1,2-dibromoethane as the quaternizing agent led only to the isolation N-(2-bromoethyl)thiazolium bromide; however, 1,3-bis(4,5-dimethyl-3-thiazolio)ethane dichloride (compound 4-2, Cl instead of Br) was prepared by "construction", that is to say, by reaction of 3-chloro-2-butanone with N,N'-dithioformylethylendiamine (prepared from ethylendiamine[21]). The resulting salts were easily isolated and purified with the sole exception of compound 4-7 the high hygroscopicity of which made its manipulation difficult. All of them were soluble in methanol and insoluble in chloroform.



4 **5**

Figure

Some of these bridged salts were studied by NMR under the conditions described by Jordan[13]. For instance, the 1,2-bis(4,5-dimethyl-3-thiazolio)propane dibromide shows, in DMSO solution, a peak at 156.1 ppm, corresponding to the two equivalents carbon atoms 2 and 2' (see Figure), and two more signals at 142 and 133.2 ppm due to the two couples of equivalent carbon atoms 4-4' and 5-5'. When sodium hydride is added such peaks disappear and appear a new set of signals at 136 and 128.4 ppm corresponding to quaternary carbon atoms 4-4' and 5-5', displaced at higher field because the disappearance of the charge in the formation of the bis(thiazolin-2-ylidene) system (type 2 structure), and a clear signal appears (carbon 2 and 2') at 114 ppm, in excellent concordance with the value described by Jordan for the, so called, "symmetric dimer" or bis(thiazolin-2-ylidene)s; this is the demonstration of the formation of the bis(thiazolin-2-ylidene) in basic conditions from bridged thiazolium salts as the sole product observed.

The second part of our work has determined the activity of the new salts in the benzoin condensation. Such activity was measured in terms of yield of benzoin, determined by g.l.c., working under the same strictly controlled conditions already employed in our desilylation study of 3-methyl-2-(trimethylsilyl)benzothiazolium trifluoromethanesulphonate.[19] Yields are collected in the Table together with those from control experiments using the simple salts (**6**) [3,4,5-trimethylthiazolium (**1**, R_1=R_2=R_3= CH_3) iodide] and (**7**) [3-methylbenzothiazolium (**1**, R_1= CH_3, R_2-R_3= CH=CH-CH=CH) iodide].

Table. Benzoin condensation catalytic activity of 3,3'-polymethylene-bridge thiazolium salts plus bases.

salt	A	B	salt	A	C
6	69.2	27.5	**7**	4.0	4.4
4-2	37.0				
4-3	59.2	35.4	**5-3**	0.8	1.8
4-4	13.8	0	**5-4**	1.3	0.9
4-5	39.7	7.6	**5-5**	15.4	11.0
4-6	44.2	6.5	**5-6**	26.8	14.7
4-7	64.9	7.9	**5-7**	11.7	2.1
4-8	2.3	1.4	**5-8**	1.4	4.3

Gas-chromatographic benzoin quantification was realized using a Hewlett-Packard 5890 chromatograph fitted with a Hewlett-Packard 19091/102 high-performance capillary cross-linked column, 5% phenylmethylsilicone, 25 m, 0.2 mm internal diameter. A temperature program of 90 °C for 2 min and then 16 °C/min up to 300 °C and decanol as internal standard were employed. Reaction conducted under the following conditions: A) 4.9 mmol of benzaldehyde; 0.49 mmol salt (0.98 for **6** and **7**); 1.4 mmol of diisopropylethylamine; 5 mL anh. dioxane; 101 °C; 24 h.; argon atm. B) 4.9 mmol of benzaldehyde; 0.05 mmol salt (0.1 for **6**); 0.14 mmol of diisopropylethylamine. Working conditions as in A). C) Conditions as in A) but changing refluxing dioxane by refluxing ethanol.

This very clear dependency observed between yields and length of the polymethylene bridge supports our views on the relevant protagonism of bis(thiazolin-2-ylidenes)s as the catalytic species, because in the present case their formation gives rise to diaza-ring formation. The results show a clear dependency on the relationship between size and properties (stability, ease of formation, etc.,) of a ring. Observe that in the best cases, the yields are better than that obtained using the conventional salts of reference.

Conclusion

From the former results we conclude that the present benzoin condensation experiments using 3,3'-polymethylene-bridged thiazolium salts (plus bases) as catalysts confirm our view that the actual catalytic species in the benzoin condensation and related processes are the bis(thiazolin-2-ylidene)s **2**.

Acknowledgment

We acknowledge gratefully the support of the Spanish Ministerio de Educación y Ciencia through a grant (PB87-0166) and a direct scholarship (to J. M.).

References

(1) (a) Lapworth, A. J., *J. Chem. Soc.* **1903**, *83*, 995-1005. (b) Lapworth, A. J., *J. Chem. Soc.* **1904**, *85*, 1206-1214.

(2) (a) Bredig, G.; Stern, E., *Z. Electrochem.* **1904**, *10*, 582-587. (b) Stern, E., *Z. Phys. Chem.* **1905**, *50*, 513-559.

(3) Knebrich, J.P.; Schowen, R.L.; Wang, M.; Lupes, M.E., *J. Am. Chem. Soc.* **1971**, *93*, 1214-1220.

(4) Ugai, T.; Tanaka, R.; Dokawa, T., *J. Pharm. Soc. Jpn.* **1943**, *63*, 296-300.

(5) Ugai, T.; Dokawa, T.; Tsubokawa, S., *J. Pharm. Soc. Jpn.* **1944**, *64*, 7A, 3-4.

(6) Lachmann, B.; Steinmaus, H.; Wanzlick, H. W., *Tetrahedron* **1971**, *27*, 4085-4090.

(7) Lappert, M. F.; Maskell, R. K., *J. Chem. Soc., Chem. Commun.* **1982**, 580-581.

(8) Breslow, R., *J. Am. Chem. Soc.*, **1958**, *80*, 3719-3726.

(9) Wanzlick, H.W.; Kleiner, H.J., *Angew. Chem.* **1963**, *75*, 1204.

(10) Metzger, J.; Larivé, H.; Dennilauler, R.; Baralle, R.; Gaurat, C., *Bull. Soc. Chim. Fr.* **1964**, 2857-2867.

(11) Quast, H.; Hünig, S., *Angew. Chem.* **1964**, *76*, 989-990.

(12) Quast, H.; Hünig, S., *Chem. Ber.* **1966**, *99*, 2017-2038.

(13) Yao-Tsung, Chen ; Jordan, F., *J. Org. Chem.* **1991**, *56*, 5029-5038.

(14) Wanzlick, H.W.; Esser, F.; Kleiner, H.J., *Chem. Ber.* **1963**, *96*, 1208-1212.

(15) Wanzlick, H. W.; Kleiner, H.J.; Lasch, I.; Fuldner, H.U.; Steinmaus, H., *Ann. Chem.* **1967**, *708*, 155-169.

(16) Krasuki, W.; Regitz, M., *Z. Naturforsch.* **1984**, *39b*, 1806-

(17) Golbik, R.; Neef H.; Hübner, G.; König, S.; Seliger, B.; Meshalkina, L.; Kochetov, G.A.; Schellenbeerger, A., *Bioorganic Chemistry* **1991**, *19*, 10-17.

(18) Tatsuya Nabeshima; Kazuhiko Moriyama; Yumihiko Yano, *J. Chem. Soc., Chem. Comm.* **1991**, 373-374.

(19) Castells, J.; López-Calahorra, F.; Domingo, L., *J. Org. Chem.* **1988**, *53*, 4433-4436.

(20) Some α,ω-bis(3-benzothiazolio)alkane salts are mentioned without any comment on their preparation and properties in Bass, J.D., *Research Disclosure* **1975**, 33-36. Analogously, α,ω-bis(3-thiazolio)alkane in Inoue, H.; Tamura, S., *J. Chem. Soc., Chem. Commun,* **1985**, 141-142.

(21) Stowell, J.C.; Ham, B.H.; Esslinger, M.A.; Duplantier, A.J. *J. Org. Chem.* **1989**, *54*, 1212-1213.

(Received in UK 17 September 1992)