

## Crossed Aldol Type Condensation Reactions in Aqueous Media

T. H. Chan,\* C. J. Li, and Z. Y. Wei

*Department of Chemistry, McGill University, Montreal, Quebec, Canada H3A 2K6*

Directed crossed aldol type condensations can be carried out in aqueous media using  $\alpha$ -halocarbonyl compounds, aldehydes, and metallic zinc or tin.

---

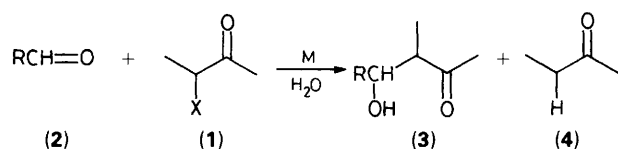
The aldol condensation is one of the most important reactions for forming carbon-carbon bonds.<sup>1</sup> However, under the classical aldol reaction conditions involving basic media, dimers, polymers, self-condensation products, or  $\alpha$ ,  $\beta$ -unsaturated carbonyl compounds are invariably formed as well. The

formation of these products is often attributed to the fact that the aldol condensation is an equilibrium process.<sup>2</sup> Useful modifications of the classical aldol condensation, especially using Lewis acid promoted reactions of enol, silyl, or tin ethers with carbonyl compounds,<sup>3,4</sup> have been developed to alleviate

**Table 1.** Crossed aldol type reactions in aqueous media.

Entry	$\alpha$ -Halocarbonyl (1) (equiv.)	Aldehyde (2) (equiv.)	Reaction conditions Metal (equiv.); temp./°C; time/h	Product			Recovered material/equiv.	
				(3)/ % yield	erythro: threo	(4) equiv.	(1)	(2)
1	PhCOCHMeBr (1.0)	PhCHO (1.0)	Sn (1.0); 70; 4	41	—	0.49	0.10	0.59
2	PhCOCHMeBr (1.0)	PhCHO (1.0)	Sn (1.0); 85; 4	0	—	1.0	0	1.0
3	PhCOCHMeBr (1.5)	PhCHO (1.0)	Zn (4.0); <sup>a</sup> ; 2	76	—	0.12 <sup>b</sup>	c	c
4	PhCOCHMeBr (1.0)	n-C <sub>8</sub> H <sub>17</sub> CHO (1.0)	Sn (1.0); 75; 3	57	—	0.43	—	0.43
5	PhCOCHMeBr (1.5)	PhCHO (1.0)	Zn (4.0); <sup>a</sup> ; 2	82	71:29	0.68	—	c
6	PhCOCHMeBr (1.5)	Me <sub>2</sub> CHCHO (1.0)	Zn (4.0); <sup>a</sup> ; 2	74	45:55	0.76	—	c
7	PhCOCHMeBr (1.5)	c-C <sub>6</sub> H <sub>11</sub> CHO (1.0)	Zn (4.0); <sup>a</sup> ; 2	83	40:60	0.67	—	c
8	PhCOCHMeBr (1.5)	n-C <sub>8</sub> H <sub>17</sub> CHO (1.0)	Zn (4.0); <sup>a</sup> ; 2	87	64:36	0.63	—	c
9	PhCOCHMeBr (1.5)	n-C <sub>3</sub> H <sub>7</sub> CHO (1.0)	Zn (4.0); <sup>a</sup> ; 2	80	68:32	0.70	—	c
10	PhCOCHMeBr (1.0)	PhCHO (1.0)	Sn (1.0); 80; 4	67	47:53	0.33	—	0.33
11	PhCOCHMeBr (1.0)	c-C <sub>6</sub> H <sub>11</sub> CHO (1.0)	Sn (1.0); 80; 4	83	64:36	0.17	—	0.17
12	PhCOCH <sub>2</sub> Br (1.0)	PhCHO (1.0)	Sn (1.0); 80; 4	64	—	0.36	—	0.36
13	PhCOCH <sub>2</sub> Br (1.5)	PhCHO (1.0)	Zn (4.0); <sup>a</sup> ; 2	85	—	0.65	—	c
14	MeCOCHMeBr (1.5)	PhCHO (1.0)	Zn (4.0); 35; 2	71	61:39	0.79	—	0.29
15	MeCH <sub>2</sub> COCH <sub>2</sub> Br (1.5)	PhCHO (1.0)	Zn (4.0); 35; 2	72	—	0.78	—	0.28
16	MeCOCHMeBr (1.0)	PhCHO (1.0)	Sn (1.0); 80; 4	85	—	<sup>d</sup>	<sup>d</sup>	0.16
17	MeCH <sub>2</sub> COCH <sub>2</sub> Br (1.0)	PhCHO (1.0)	Sn (1.0); 80; 4	17	—	<sup>d</sup>	<sup>d</sup>	0.83
18	MeCOCHMeBr (1.5)	n-C <sub>8</sub> H <sub>17</sub> CHO (1.0)	Zn (4.0); 35; 2	0	—	<sup>d</sup>	<sup>d</sup>	1.0
19	MeCOCH <sub>2</sub> Cl (1.5)	PhCHO (1.0)	Zn (4.0); 35; 2	63	—	<sup>d</sup>	<sup>d</sup>	0.37

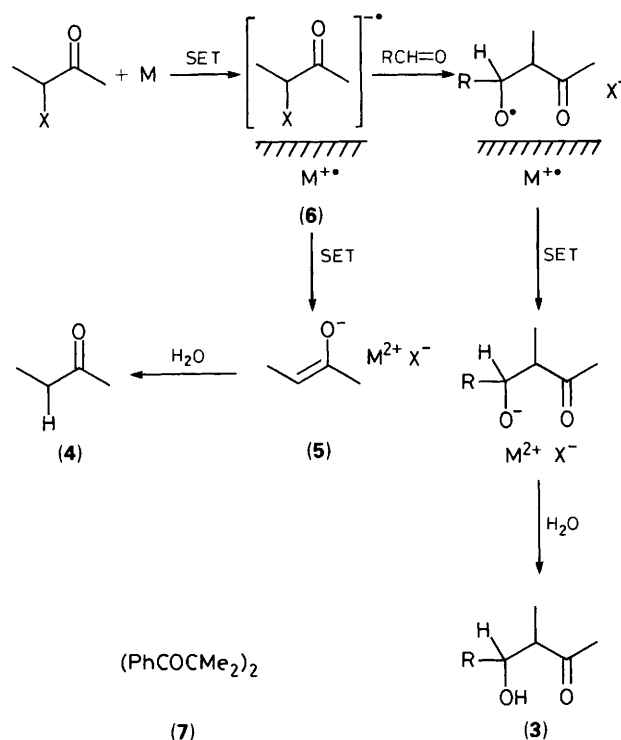
<sup>a</sup> Room temp. <sup>b</sup> (PhCOCHMe)<sub>2</sub> (7) was obtained, 0.67 equiv. <sup>c</sup> Amount of recovered starting material was not determined. <sup>d</sup> The amount of reduced product (4) was not determined due to low b.p. of (4).



these difficulties. These modifications typically employ an organic solvent as the reaction medium.

We report here that directed crossed aldol type reactions can be carried out in aqueous media. These reactions involve  $\alpha$ -halocarbonyl compounds as one component, and aldehydes as the other component, using metallic zinc or tin to promote the reaction in water (Scheme 1). Typically, zinc dust (4.0 mmol) or tin powder (1.0 mmol) was added to a mixture of an  $\alpha$ -halocarbonyl compound (1) (1.0–1.5 mmol) and an aldehyde (2) (1.0 mmol) in water (5 ml). The reaction mixture was stirred at the appropriate temperature for 2–4 h, then quenched with ether. The ether solution was dried, evaporated, and the crude product purified by flash chromatography to give the products (3) and (4).

The results, summarized in Table 1, suggest that the crossed aldol type condensation product (3) is not formed *via* the classical metal enolate intermediate (5). This conclusion is based on the following observations. Firstly, product (3) is not accompanied by the usual side products from self-condensation of the aliphatic aldehydes expected from metal enolate chemistry in aqueous media (entries 4, 6–9, 11). Secondly, the reactions of 1-bromobutan-2-one or its regioisomer 3-bromobutan-2-one with benzaldehyde were regioispecific in giving the appropriate crossed aldol type products without trace of the regioisomers (entries 14, 15 and 16, 17). A metal enolate intermediate would be expected to equilibrate in aqueous medium to give the various regioisomeric enolates.



Thirdly, the reduction product (4), which is more likely to be derived from the metal enolate (5), was formed by a pathway apparently different from that giving the crossed aldol product (3). For example, in the reaction of 2-bromo-2-methyl-1-phenylpropan-1-one with benzaldehyde and tin at 70 °C (entry 1), the aldol product (3) was formed together with the reduction product (4). On the other hand, when the same reaction was carried out at a temperature of 85 °C, only the

reduced product (4) was obtained (entry 2). A possible reaction mechanism, invoking the intermediacy of a radical anionic species (6), is outlined in Scheme 2, in which the critical carbon-carbon bond formation occurs prior to the formation of the free metal enolate, possibly at the metal surface. In support of this mechanism, compound (7) was obtained as a minor product in the reaction of 2-bromo-2-methyl-1-phenylpropan-1-one with benzaldehyde (entry 3). Compound (7) is most likely derived from the coupling of the radical intermediate.

The present condensation reaction showed interesting chemoselectivity. Condensations between  $\alpha$ -bromoalkyl aryl ketones with aldehydes proceed quite well, but  $\alpha$ -halo aliphatic ketones condense only with aryl aldehydes and not

with aliphatic aldehydes (entry 18). This is again quite different from the reactions of, for example, tin(II) enolates in organic solvents.<sup>3</sup>

*Received, 30th November 1989; Com. 9/05124D*

### References

- 1 H. O. House, 'Modern Synthetic Reactions,' 2nd edn., W. A. Benjamin, New York, 1972.
  - 2 T. Mukaiyama, *Isr. J. Chem.*, 1984, **24**, 162.
  - 3 T. Mukaiyama, *Org. React.*, 1982, **28**, 203.
  - 4 R. W. Stevens, N. Iwasawa, and T. Mukaiyama, *Chem. Lett.*, 1982, 1459.
-