

INTERMOLECULAR DEHYDRATION BETWEEN CARBOXYLIC ACIDS AND ALCOHOLS BY THE USE OF DIETHYL AZODICARBOXYLATE AND 3-METHYLBENZOTHAZOLE-2-SELONE<sup>1)</sup>

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The reaction of carboxylic acids with alcohols in the presence of diethyl azodicarboxylate and 3-methylbenzothiazole-2-selone gave the corresponding esters with retention of configuration at the alcoholic carbon atom.

Diethyl azodicarboxylate (DEAD) reacts with trivalent phosphorus compounds and with thiocarbonyl compounds to give betaines and 1:1 adducts, respectively.<sup>2)</sup> These facts indicate that DEAD has phosphophilicity and thiophilicity. It could therefore be assumed that DEAD has also considerable affinity to group VIB elements. Thus, 3-methylbenzothiazole-2-selone (MBTSe) would be expected to react with DEAD forming a betaine (1) which functions as activating reagent of carboxylic acids and/or alcohols.

Benzoic acid expectedly reacted with 2-phenylethanol in the presence of equimolar amounts of DEAD and MBTSe in tetrahydrofuran (THF) under argon at room temperature for 4 d to give 2-phenylethyl benzoate (35%), 3-methylbenzothiazol-2-one (95%), and selenium (86%) with 43% recovery of the starting alcohol. The yield of 2-phenylethyl benzoate increased to 42%, when the reaction was carried out under reflux for 10 h. The reaction of 2-phenylethanol with two molar amounts each of benzoic acid, DEAD, and MBTSe in the presence of a catalytic amount of N,N-dimethylaniline (DMA) in THF under reflux for 9 h afforded 2-phenylethyl benzoate in 79% yield (Table 1; entry 1). Under the same conditions, benzoic acid reacted with butanol and 2-octanol to give butyl benzoate and 2-octyl benzoate in 61% and 28% yields, respectively (Table 1; entries 2 and 3).

Propionic acid, 2-butenic acid, and phenylacetic acid were also reacted with 2-phenylethanol in the presence of DEAD and MBTSe giving the corresponding esters in 44%, 57%, and 90% yields, respectively (Table 1; entries 5, 6, and 7).

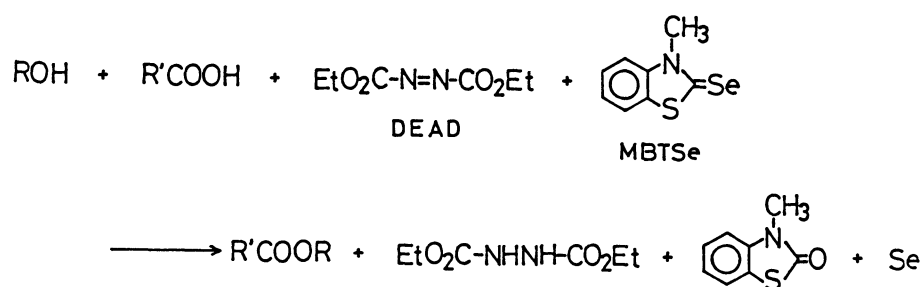
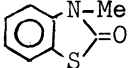


Table 1. Reaction of Alcohols with Carboxylic Acids, DEAD, and MBTSe in THF under Reflux<sup>a)</sup>

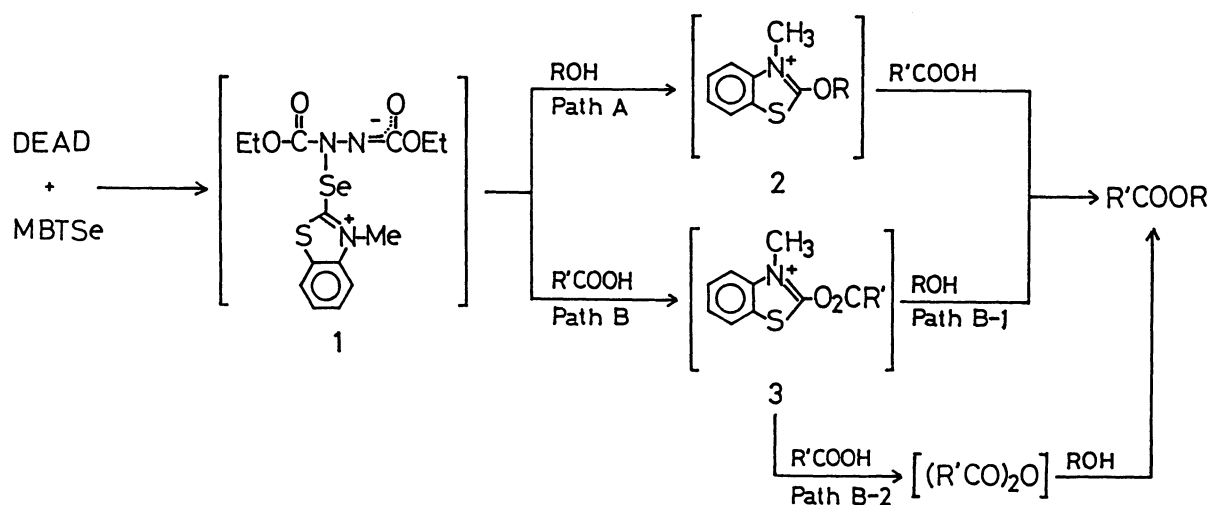
Entry	Reactants and catalyst			Reaction time / h	Yields of products / %	
	ROH R	R'COOH R'	Cat. <sup>b)</sup>		R'COOR	
1	PhCH <sub>2</sub> CH <sub>2</sub> -	Ph-	DMA	9	79	85
2	C <sub>4</sub> H <sub>9</sub> -	Ph-	DMA	9	61	76
3	C <sub>6</sub> H <sub>13</sub> (CH <sub>3</sub> )CH-	Ph-	DMA	9	28	78
4	(CH <sub>3</sub> ) <sub>3</sub> C-	Ph-	DMA	9	0	97
5	PhCH <sub>2</sub> CH <sub>2</sub> -	C <sub>2</sub> H <sub>5</sub> -	DMA	9	44	68
6	PhCH <sub>2</sub> CH <sub>2</sub> -	CH <sub>3</sub> CH=CH-	DMA	9	57	80
7	PhCH <sub>2</sub> CH <sub>2</sub> -	PhCH <sub>2</sub> -	DMA	9	90	74
8	C <sub>6</sub> H <sub>13</sub> (CH <sub>3</sub> )CH-	PhCH <sub>2</sub> -	DMA	8	52	55
9	C <sub>6</sub> H <sub>13</sub> (CH <sub>3</sub> )CH-	PhCH <sub>2</sub> -	MIm	8	55	40
10	C <sub>6</sub> H <sub>13</sub> (CH <sub>3</sub> )CH-	PhCH <sub>2</sub> -	Tet	8	33	38

a) Molar ratio of ROH : R'COOH : DEAD : MBTSe is 1 : 2 : 2 : 2.

b) DMA = N,N-Dimethylaniline; MIm = N-Methylimidazole; Tet = Tetrazole.

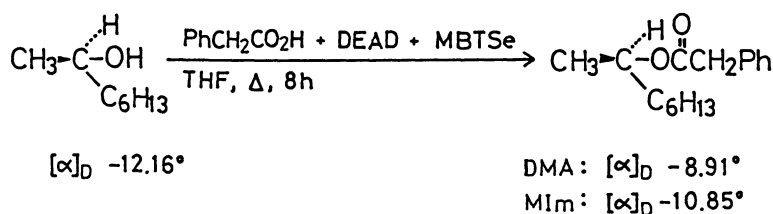
Since N-methylimidazole (MIm) is known as an effective catalyst for the condensation of alcohols with acidic components, the reaction of phenylacetic acid with 2-octanol was carried out in the presence of MIm and tetrazole.<sup>3)</sup> As shown in Table 1 (entries 9 and 10), however, no considerable effect of the azoles could be observed.

The present reaction would be explained by assuming the initial formation of betaine (1) which in turn reacts with either an alcohol or a carboxylic acid giving 2-alkoxy-3-methylbenzothiazolium salt (2; path A) or 2-acyloxy-3-methylbenzothiazolium salt (3; path B). Mukaiyama et al. have reported that acyloxy- and alkoxy-onium



salts of aza-arenes are reactive acylating and alkylating reagents for a variety of nucleophiles.<sup>4)</sup> Thus, intermediate 2 or 3 has once been formed in the reaction system, they react respectively with acidic or alcoholic component to afford the corresponding esters (path A and path B-1). Instead of direct acylation of alcohol by 3, intermediacy of acid anhydride is also conceivable (path B-2).

The alkylation of nucleophiles by 2-alkoxy-3-ethylbenzothiazolium salt has been demonstrated to proceed through the inversion of the configuration at the alkyl group.<sup>4)</sup> In order to elucidate the mechanism of the present reaction, therefore, the esterification of an optically active alcohol was attempted. When (R)-(-)-2-octanol (optical purity; 85%)<sup>5)</sup> was allowed to react with phenylacetic acid, DEAD, and MBTSe in the presence of a catalytic amount of DMA under the same conditions shown in Table 1 (entry 8), 2-octyl phenylacetate with  $[\alpha]_D -8.91^\circ$  (c 1.83, CHCl<sub>3</sub>) was obtained. Since (R)-(-)-2-octyl phenylacetate prepared by the reaction of the (R)-(-)-2-octanol with phenylacetyl chloride exhibited  $[\alpha]_D -11.24^\circ$  (c 1.93, CHCl<sub>3</sub>), the condensation using DEAD and MBTSe proceeded with 90% retention of the configuration. When MIm was used as a catalyst, the reaction took place with practically complete retention of the configuration. These results suggest that the present reaction involves a carboxylic acid activation process.



Although the reaction mechanism has not yet been elucidated, the reaction described in this paper suggests interesting possibilities for further works.

The general procedure is as follows. A solution of (R)-(-)-2-octanol (3 mmol,  $[\alpha]_D -12.16^\circ$  (c 1.53, heptane), optical purity; 85%),<sup>5)</sup> phenylacetic acid (6 mmol), MBTSe (6 mmol), DEAD (6 mmol), and MIm (0.6 mmol) in THF (15.5 ml) was refluxed under  $N_2$  for 8 h. Precipitated selenium was filtered off and the filtrate was evaporated. Benzene was added to the residue, heated to dissolve precipitate, and allowed to cool to room temperature. Diethyl hydrazinedicarboxylate was filtered off and the filtrate was washed with 10%  $NaHCO_3$ . Organic layer was separated, dried ( $MgSO_4$ ), and evaporated. The residue was applied on silica gel plates (Merck PF<sub>254</sub>) and developed by ether-petroleum ether (1 : 5) giving 2-octyl phenylacetate (306 mg, 41%) which was purified by distillation (Kugelrohr, 100-132 °C/0.3-0.4 Torr:  $[\alpha]_D -10.85^\circ$  (c 2.23,  $CHCl_3$ )).

#### References

- 1) This work has been presented in part at the 29th IUPAC congress, June 9, 1983, Cologne.
- 2) O. Mitsunobu, *Synthesis*, 1981, 1
- 3) See for example, V. A. Efimov, S. V. Reverdatto, and O. G. Chakhmakhcheva, *Tetrahedron Lett.*, 23, 961 (1982), and refs. therein.
- 4) T. Mukaiyama, *Angew. Chem. Int. Ed. Engl.*, 18, 707 (1979).
- 5) O. Mitsunobu, M. Wada, and T. Sano, *J. Am. Chem. Soc.*, 94, 679 (1972), and ref. therein.

(Received February 29, 1984)