Benzylation of Carboxylic Acids by Oxidation-Reduction Condensation Using Quinones and Benzyloxydiphenylphosphine

Teruaki Mukaiyama,* Taichi Shintou, and Wataru Kikuchi

The Kitasato Institute, Center for Basic Research, TCI, 6-15-5, Toshima, Kita-ku, Tokyo 114-0003

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Various carboxylic benzyl esters were obtained in high yields by way of oxidation-reduction condensation in which benzyloxydiphenylphosphine (BDPP), having been prepared easily from chlorodiphenylphosphine and benzyl alcohol, was treated with various carboxylic acids in the presence of 2,6-dimethyl-1,4benzoquinone(DMBQ) under mild conditions.

The fundamental concept of oxidation-reduction condensation is to perform dehydration condensation with removal of H₂O as 2[H] and [O] by using a combination of weak reductant and oxidant. For example, several acylating reactions were carried out by using combinations of diphenylmercury and tri-nbuthylphosphine,¹ trans-dibenzoylethylene and tri-nbutylphosphine,² and 2,2'-dipyridyl disulfide and phosphine.³ Preparation of phosphoric esters was also carried out by using (EtO₃)P and diethyl azodicarboxylate in the presence of alcohols.⁴ Mitsunobu developed this concept into the efficient alkylation methods by using a combination of triphenylphosphine and diethyl azodicarboxylate (DEAD) and achieved condensation reaction between alcohols and various nucleophiles, which is a method widely known as Mitsunobu reaction.⁵ Recently, Tsunoda et al. reported alkylating reaction which took place likewise bv using alcohols and cyanomethylenetributylphosphorane.⁶ Here, we would like to describe highyielding preparation of carboxylic benzyl esters by way of new type oxidation-reduction condensation using benzyloxydiphenylphosphine, carboxylic acids and 2,6-dimethyl-1, 4-benzoquinone under mild conditions.

In the first place, benzylation of benzoic acid with 1.0 equiv of BDPP⁷ was tried by using 1.0 equivalent of trans-dibenzoylethylene in dichloromethane, and the desired product was obtained in 55% yield within 3 h (Table 1, entries 1,2). When DEAD was used under the above conditions, carboxylic benzyl ester was then obtained in 73% yield (entry 3). On the other hand, the carboxylic esters were not obtained even when powerful oxidizing agents as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), tetrachloro-1,4-benzoquinone (p-chloranil) and 2,6dichloro-1,4-benzoquinone were used (entries 4–6). On the contrary, the desired product was obtained in 75% yield when a milder oxidant such as 1,4-benzoquinone was used under the above conditions (entry 7). After screening several oxidants, the benzyl carboxylic ester was found to be obtained in 90% yield under milder conditions when DMBQ was used (entries 8–16).

While benzyloxydialkylphosphines, e.g. benzyloxydiisopropylphosphine or benzyloxydicyclohexylphosphine, afforded the desired ester in 60% and 57% yields, respectively, BDPP afforded the ester effectively in 90% yield (Table 2, entries 1–3). The reaction proceeded rapidly (0.5 h) and the ester was still more obtained in 98% yield when 1.1 equivalent of BDPP was used
 Table 1. Screening of quinone derivatives on benzylation of benzoic acid

DhC	Pr Qu	n ₂ POBn (1.0 e inone (1.0 eq	PhCOOP		
$CH_2Cl_2, rt, 3 h$			h	PhCOOBh	
Entry	Quinone	Yield /%	Entry	Quinone	Yield /%
1	none	N.R.	9		D 66
2	O = Ph	D 55	10) 12
3) 73	11		e) 45
4) N.R.	12		5) 70
5) N.R.	13) 19
6) N.R.	14) 77
7	0=	D 75	15		D 19
8	o=<) 90	16) 32

(entries 3-7).

The benzylation of several carboxylic acids using BDPP and DMBQ was then tried (Table 3). As a result, esterification of various carboxylic acids smoothly proceeded to afford the corresponding carboxylic esters in high yields under mild conditions. In the case of *N-tert*-butoxycarbonyl-L-valine, the corresponding benzyl ester was obtained exclusively and no epimerization was observed.⁸

A proposed reaction mechanism is shown in Scheme 1: BDPP initially reacted with DMBQ to form adduct **1**, which was

 Table 2. Effect of substituents of phospine on benzylation of benzoic acid

PhCOOH	DMI CH	$\begin{array}{c} R_2 POBn \\ \hline 3Q(1.0 \text{ equiv.}) \\ \hline _2 Cl_2, \text{ Time, rt} \end{array}$	PhCOOBn	
Entry	R	R ₂ POBn /equiv	Time /h	Yield /%
1	ⁱ Pr	1.0	3	60
2	cyclohexyl	1.0	3	57
3	Ph	1.0	3	90
4	Ph	1.1	3	97
5	Ph	1.3	3	97
6	Ph	1.1	0.5	98
7	Ph	1.1	1	97

Table 3. Benzylation of carboxylic acids with BDPP andDMBQ

BCOOH	Ph ₂ POBn(1.1 equiv.) DMBQ(1.0 equiv.)	BCOOBn
	CH ₂ Cl ₂ , rt, 0.5 h	Посовл
Entry	Carboxylic Acid	Yield /%
1	Соон	98
2	— соон	98
3	МеО-СООН	95
4	02N-СООН	95
5	PhCOOH	93
6	СООН	89
7	^t BuCOOH	89
8	Сосон	86
9		90 ^a

^a Determined by HPLC using Daicel CHIRALPAK AF.⁸



in turn transformed to the phosphonium carboxylate 2 by the interaction with carboxylic acid. Intramolecular attack of the carboxylate anion to the benzylic carbon of the salt 2 afforded the

corresponding carboxylic acid ester along with diphenylphosphiric acid 4-hydroxy-3,5-dimethylphenyl ester **3**. The key intermediate of this new oxidation-reduction condensation is different from that of Mitsunobu reaction that involves alkoxyphosphonium carboxylate.⁹

Typical experimental procedure is as follows: to a mixture of carboxylic acid (0.60 mmol) and 2,6-dimethyl-1,4-benzoquinone (0.60 mmol) under argon atmosphere was added a solution of benzyloxydiphenylphosphine (0.66 mmol) in dichloromethane (0.50 ml) at room temperature. The reaction mixture was stirred for 0.5 h at room temperature. On completion of the reaction (detected by TLC), it was quenched with water and the mixture was extracted with dichloromethane. The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by preparative TLC to afford the corresponding benzyl esters in high yields.

Thus, a new and efficient method for the benzylation of carboxylic acid was established by way of oxidation-reduction condensation on treating benzyloxydiphenylphosphine and milder oxidizing agent such as DMBQ, followed by the reaction with carboxylic acid. Thus, the corresponding carboxylic esters were obtained in excellent yields under mild conditions. Further study on this type of condensation reaction is now in progress.

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References and Notes

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- 7 The equimolar amounts of chlorodiphenylphosphine and benzyl alcohol were mixed with the equimolar amounts of pyridine in diethyl ether at room temperature under argon atmosphere. Distillation gave colorless oil, Yield 55% (bp. 155–157 °C/0.2 mmHg). See: B. A. Arbouzov and N. P. Grechkin, *Zh. Obshch. Khim.*, **20**, 107 (1950).
- 8 HPLC (Daicel Chiralpak AF, $hexane/{}^{l}$ PrOH = 19/1, flow rate = 1.0 ml/min): ${}^{t}R$ = 7.8 min (L-valine derivative), ${}^{t}R$ = 9.6 min (D-valine derivative). *N-tert*-butoxycarbonyl-D-valine afforded the corresponding benzyl ester in 89% yield and no epimerization took place.
- 9 The reaction of benzoic acid with 1.1 equivalent of benzyl alcohol and triphenylphosphine was tried by using 1.0 equivalent of BDMQ in dichloromethane at room temperature, but the desired product was not obtained.