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KOH-promoted synthesis of oxirane functional derivatives from diethyl bromomalonate and aldehydes under phase-transfer catalysis conditions

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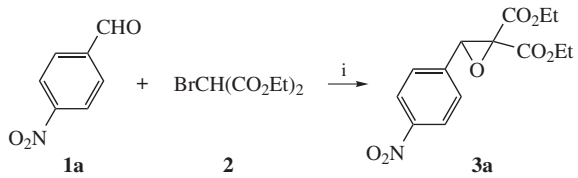
The Darzens condensation of diethyl bromomalonate with aromatic or isoprenoid aldehydes under heterogeneous conditions (KOH/MeCN) in the presence of Bu_4NPF_6 as a recoverable phase-transfer catalyst afforded the corresponding diethyl 3-R-oxirane-2,2-dicarboxylates in high yields.

Oxirane-2,2-dicarboxylates are the valuable intermediates in the synthesis of natural compounds containing dihydrofuran (*e.g.*, furanomycin, cryptoresinol)[1] or tetrahydrofuran (indole alkaloids)[2] fragments and can be used as protease inhibitors.[3] They are commonly prepared by epoxidation of methylidenemalonates with some inorganic (H_2O_2,[4] sodium hypochlorite[5]) or organic (mCPBA,[6] oxidoiodanes,[7] TADOOH[8]) oxidants, or by the reactions of aldehydes with carbenes generated *in situ* from dialkyl diazomalonates[9] or iodonium ylides,[10] their yields being significantly substrate dependent.

A well-recognized method to access oxiranes is the Darzens condensation of carbonyl compounds with α-halogenocarboxylic acid derivatives. It can be efficiently processed under heterogeneous conditions in the presence of phase-transfer catalysts (PTC), in particular those immobilized on a polymer matrix (polymer-supported PTC).[11] Surprisingly, just three examples of the use of bromomalonic esters as starting compounds in this reaction have been reported so far. In 1983[12] some of us unexpectedly obtained 3-substituted oxirane (50% yield) in the reaction of β,β-dichloroacrolein or its vinylogue with diethyl bromomalonate under PTC-conditions. The K_2CO_3-promoted condensation of diethyl bromomalonate with crotonaldehyde afforded the corresponding epoxy cyclopropane derivative in 20% yield.[13] Recently,[14] the structure of diethyl 3-(pent-1-enyl)-oxirane-2,2-dicarboxylate was hypothetically assigned to an out-of-range product of cyclopropanation reaction without its confirmation by experimental data. Herein, we report a simple and efficient synthesis of 3-R-oxirane-2,2-dicarboxylates (R = Alk or Ar) **3** by a solid base-promoted (KOH) reaction of aldehydes **1** with diethyl bromomalonate **2** in the presence of an available and reusable PTC such as tetrabutylammonium hexafluorophosphate (Bu_4NPF_6).

At first, we studied the model reaction between 4-nitrobenzaldehyde **1a** and bromomalonate **2** in acetonitrile, which had been used as the solvent in similar condensation of benzaldehydes with chloroacetic ester.[11(b)] The reaction between compounds **1a** and **2** (Scheme 1) did not occur in the presence of finely powdered solid KOH (1.2 equiv.). However, upon PTC addition (5 mol%) oxirane **3a** was formed in reasonable to high yields. Table 1 summarizes the results of four studied PTCs ($BnEt_3NCl$, Bu_4NBr, Bu_4NBF_4, and Bu_4NPF_6). Hexafluorophosphate salt Bu_4NPF_6 that had been recently recognized as an efficient reusable PTC[15] exhibited the best catalytic performance. Importantly, it is nearly insoluble both in water and in Et_2O[11(a),(b)] and this solubility profile allowed us to completely recover the PTC by simply filtrating it off the Et_2O/water two-phase mixture during the work-up procedure† and reuse it three times in the model reaction with no noticeable disprovement of the reaction rate or product yield (Table 1, entry 5).



Scheme 1 *Reagents and conditions*: i, KOH (1.2 equiv.), PTC (5 mol%), MeCN, 20 °C, 3 h.

Table 1 Comparison of various PTCs in the reaction between **1a** and **2**.

Entry	PTC	Isolated yield of **3a** (%) [cycle]	Catalyst recovery (%) [cycle]
1	—	0	—
2	$BnEt_3NCl$	74	0
3	Bu_4NBr	83	0
4	Bu_4NBF_4	87	55
5	Bu_4NPF_6	94 [1], 94 [2], 95 [3]	95 [1], 93 [2], 92 [3]

Benzaldehydes **1a–f** bearing either acceptor or donor substituents in the aromatic ring and isoprenoid aldehydes **1g**,**h** reacted similarly to afford the corresponding oxiranes **3a–h** (Scheme 2). The yields of products **3** were comparable with (in case of **3a**) or higher than (in case of **3b–d**,**g**) those achieved by alternative methods (Table 2, entries 1–4,7). The yields remained high

† *General procedure for the synthesis of diethyl 3-R-oxirane-2,2-dicarboxylates* **3a–h**. Aldehyde **1a–h** (1 mmol), bromomalonate **2** (0.24 g, 1 mmol), Bu_4NPF_6 (0.02 g, 5 mol%) and MeCN (3 ml) were mixed and stirred for 30 min. Powdered KOH (0.07 g, 1.2 mmol) was added, the heterogeneous mixture was stirred at ambient temperature for the specified time. The solvent was removed under reduced pressure. Water (5 ml) and Et_2O (10 ml) were added to the residue and the solid catalyst was filtered out of the two-phase solvent system, dried in air and reused in the second run of the same or similar reaction without further purification. The organic layer was separated and the aqueous layer was extracted with Et_2O (3×5 ml). The combined organic layers were washed with water (3×5 ml), dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (SiO_2, eluent: hexane; hexane–EtOAc, 9:1) afforded analytically pure compounds **3a–h**.

For NMR spectra of compounds **3a–h**, see Online Supplementary Materials.

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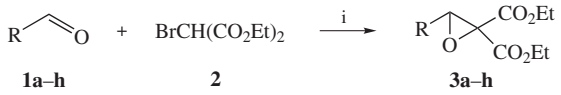


1a–h **2** **3a–h**

Scheme 2 *Reagents and conditions*: i, KOH (1.2 equiv.), Bu_4NPF_6 (5 mol%), MeCN, 20 °C.

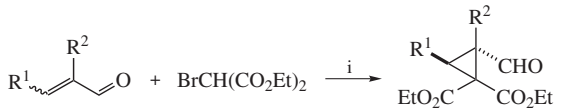
Table 2 Yields of oxiranes **3** in reactions of **1a–h** with **2**.

Entry	Aldehyde	R	*t*/h	Oxirane	Isolated yield (%)
1	**1a**	4-$O_2NC_6H_4$	6	**3a**	95 (lit.,[5] 97)[a]
2	**1b**	Ph	3	**3b**	83 (lit.,[7] 51)[b]
3	**1c**	4-ClC_6H_4	12	**3c**	89[c] (lit.,[9] 54)[d]
4	**1d**[e]	4-$MeOC_6H_4$	30	**3d**	79 (lit.,[9] 62)[d]
5	**1e**	4-$MeO_2CC_6H_4$	3	**3e**	97
6	**1f**	4-$HC(O)C_6H_4$	4	**3f**	89[c]
7	**1g**	Me_2CHCH_2	10	**3g**	78[c] (lit.,[4(a)] 58)[f]
8	**1h**	$Me_2C{=}CH(CH_2)_2C(Me){=}CH$	3	**3h**	93

[a] Data for oxidation of the corresponding diethyl arylidenemalonate with sodium hypochlorite. [b] Data for oxidation of the corresponding diethyl arylidenemalonate with oxidoiodane. [c] The reaction was carried out in the presence of PTC recovered after experiment given in the line above. [d] Data for corresponding dimethyl ester prepared by the treatment of **1** with dimethyl diazomalonate. [e] The reaction was carried out at 45 °C. [f] Data for oxidation of diethyl isopentylidene malonate with H_2O_2.

irrespective of the presence of a fresh or recovered PTC (Table 2, entries 3, 6 and 7). In the case of phthalic dialdehyde **1f**, just one of the two carbonyl groups was transformed into the oxirane unit even in experiments where an excessive amount of reactant **2** and KOH (3 equiv. of each) was used. The product **3f** contained free formyl group in the aromatic ring.

Unlike aldehydes **1a–h**, α,β-enals **4a–d** added bromomalonate **2** mainly to the electron-deficient C=C bond rather than to the conjugated carbonyl group under the herein proposed conditions to give formylcyclopropanes **5** (Scheme 3). Furthermore, we succeeded to improve selectivity of the cyclopropanation by switching from KOH to a milder deprotonating agent (LiOH or K_2CO_3) and by carrying it out in the Bu_4NPF_6/toluene heterogeneous system. This provided yields of the products **5a–d** as high as 62–70% (see Online Supplementary Materials). Substituted 1,1-dialkoxycarbonyl-2-formylcyclopropanes are valuable intermediates for the synthesis of various cyclopropane functional derivatives.[16]



4a–d **2** **5a–d**

a R^1 = Ph, R^2 = H
b R^1 = R^2 = H
c R^1 = Me, R^2 = H
d R^1 = H, R^2 = Me

Scheme 3 *Reagents and conditions*: i, K_2CO_3 (or LiOH) (1.5 equiv.), Bu_4NPF_6 (5 mol%), PhMe, 20 °C.

In summary, an efficient heterogeneous catalytic system for reactions of diethyl bromomalonate with aldehydes has been developed and its potency for the synthesis of diethyl 3-alkyl- or 3-aryloxirane-2,2-dicarboxylates has been demonstrated.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2013.01.008.

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