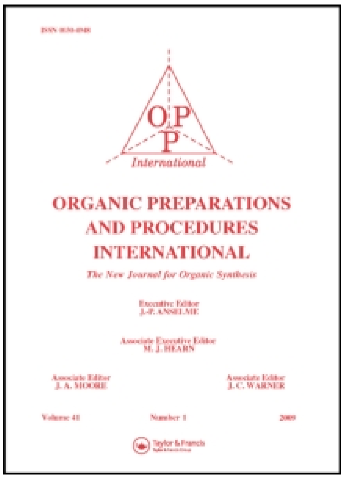

Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

PHASE-TRANSFER CATALYSED SYNTHESIS OF 4-BENZYLOXY-2-BUTANONES

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To cite this Article Guillaumet, G. , Coudert, G. and Mpassi, M.(1984) 'PHASE-TRANSFER CATALYSED SYNTHESIS OF 4-BENZYLOXY-2-BUTANONES', Organic Preparations and Procedures International, 16: 1, 42 — 47

To link to this Article: DOI: 10.1080/00304948409356166

URL: http://dx.doi.org/10.1080/00304948409356166

PHASE-TRANSFER CATALYSED SYNTHESIS OF 4-BENZYLOXY-2-BUTANONES

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(10/23/83)

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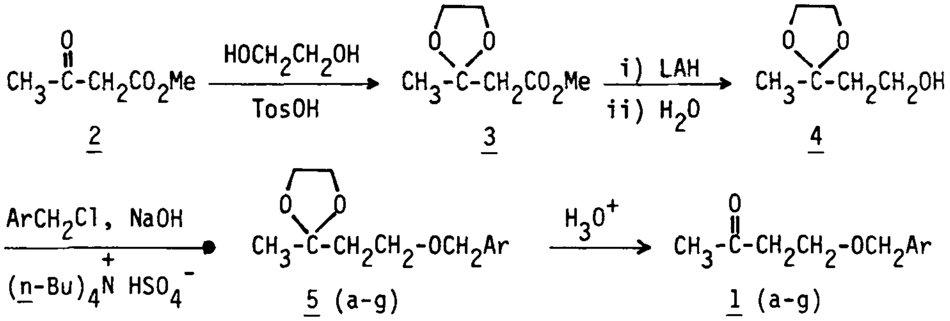
In connection with other synthetic work, we were interestted in preparing various 4-benzyloxy-2-butanones (1), substituted on the aromatic ring. The only known compound 1a was prepared by methods involving large excess of benzyl alcohol[1] and these methods could not be extended to the synthesis of compounds for which the requisite alcohols are either expensive or not readily available. We now report a general and efficient route to synthesize compounds 1 from methyl acetoacetate 2.



a) Ar = C_6H_5; b) Ar = 2-MeOC_6H_4; c) Ar = 3-MeOC_6H_4
d) Ar = 4-MeOC_6H_4; e) Ar = 2,3-diMeOC_6H_3
f) Ar = 3,4-diMeOC_6H_3; g) Ar = 2-ClC_6H_4

The keto ester 2 was first converted to the corresponding alcohol 4 by standard procedure.[2,3] The benzyl chlorides were obtained quantitatively from the corresponding alcohols.[4] Reactions of 4 with various benzyl chlorides were carried out by using liquid-liquid phase-transfer catalysis[5] to yield ethers 5 in good yields. The reaction proceeded at 40° in a 50/50 mixture of benzene and aqueous sodium hydroxide, with 1.1 equivalent of chloride derivative and 0.1 equivalent of tetrabutylammonium hydrogen sulfate. Careful hydrolysis of the acetal function was performed at room temperature in dioxane-water (50/50) in the presence of a catalytic amount of oxalic acid to yield the expected ketones 1 in high yields. A similar procedure could be performed without isolation and purification of the intermediary compounds 5.

EXPERIMENTAL SECTION

1,4-Dioxolanes (5).- Alcohol 4 (1 g, 7.5 mm), the appropriate benzyl chloride (8.25 mm) and tetrabutylammonium hydrogen sulfate (0.25 g, 0.75 mm) were dissolved in benzene (20 ml) and a 50% aqueous sodium hydroxide solution (20 ml) was then added. The reaction mixture was warmed at 40° with vigorous stirring for 6 hrs, cooled and poured into water. The aqueous phase was extracted with ether (4 x 25 ml). The organic phases were combined, washed with water, dried with magnesium sulfate and evaporated. The residual crude product 5 was purified by flash chromatography (silica gel column) before the following hydrolytic step or used directly. The yields of isolated products are based on alcohol 4.

5a, liquid (88% yield); IR neat: 1060 cm^{-1} (C-O); NMR (CCl_4): δ 1.25 (s, 3 H, CH_3), 1.88 (t, 2 H, J = 7.3 Hz, CH_2), 3.29 (t, 2 H, J = 7.3 Hz, OCH_2), 3.77 (s, 4 H, OCH_2CH_2O), 4.42 (s, 2H,

CH_2Ar), 7.24 (s, 5 H, ArH).

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.27; H, 8.11.
Found: C, 70.10; H, 8.18.

5b, liquid (84% yield); IR (neat): 1060 cm^{-1} (C-O); NMR (CCl_4): δ 1.26 (s, 3 H, CH_3), 1.92 (t, 2 H, J = 7.4 Hz, CH_2), 3.45-3.84 (m, 9 H, OCH_2, OCH_3 and OCH_2CH_2O), 4.51 (s, 2 H, CH_2Ar), 6.60-7.55 (m, 4 H, ArH).

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.67; H, 7.93.
Found: C, 66.82; H, 8.02.

5c, liquid (84% yield); IR (neat): 1050 cm^{-1} (C-O); NMR (CCl_4): δ 1.26 (s, 3 H, CH_3), 1.87 (t, 2 H, J = 7.2 Hz, CH_2), 3.44 (t, 2 H, J = 7.2 Hz, CH_2O), 3.69 and 3.75 (2 s, 7 H, OCH_3 and OCH_2-CH_2O), 4.34 (s, 2 H, CH_2Ar), 6.55-7.25 (m, 4 H, ArH).

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.67; H, 7.93
Found: C, 66.51; H, 7.84.

5d, liquid (78% yield); IR (neat): 1055 cm^{-1} (C-O); NMR (CCl_4): δ 1.25 (s, 3 H, CH_3), 1.88 (t, 2 H, J = 6.9 Hz, CH_2), 3.48 (t, 2 H, J = 6.9 Hz, CH_2O), 3.70 and 3.79 (2 s, 7 H, OCH_3 and OCH_2-CH_2O), 4.34 (s, 2 H, CH_2Ar), 6.78 (d, 2 H, J = 8.6 Hz, ArH), 7.20 (d, 2 H, J = 8.6 Hz, ArH).

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.67; H, 7.93.
Found: C, 66.83; H, 7.97.

5e, liquid (80% yield); IR (neat): 1065 cm^{-1} (C-O); NMR (CCl_4): δ 1.26 (s, 3 H, CH_3), 1.88 (t, 2 H, J = 7.3 Hz, CH_2), 3.50 (t, 2 H, J = 7.3 Hz, CH_2O), 3.73 and 3.77 (2 s, 10 H, OCH_3 and OCH_2CH_2O), 4.42 (s, 2 H, CH_2Ar), 6.60-7.05 (m, 3 H, ArH).

Anal. Calcd. for $C_{15}H_{22}O_5$: C, 63.82; H, 7.80.
Found: C, 63.74; H, 7.77.

5f, liquid (77% yield); IR (neat): 1055 cm^{-1} (C-O); NMR (CCl_4): δ 1.26 (s, 3 H, CH_3), 1.87 (t, 2 H, J = 7.0 Hz, CH_2), 3.45 (t, 2 H, J = 7.0 Hz, OCH_2), 3.6-3.9 (m, 10 H, OCH_3 and OCH_2CH_2O), 4.31 (s, 2 H, CH_2Ar), 6.6-6.8 (m, 3 H, ArH).

Anal. Calcd. for $C_{15}H_{22}O_5$: C, 63.82; H, 7.80.
Found: C, 64.02; H, 7.91.

5g, liquid (85% yield); IR (neat): 1050 cm^{-1} (C-O); NMR (CCl_4): δ 1.29 (s, 3 H, CH_3), 1.94 (t, 2 H, J = 7.2 Hz, CH_2), 3.60 (t, 2 H, J = 7.2 Hz, CH_2O), 3.80 (s, 4 H, OCH_2CH_2O), 4.51 (s, 2 H, CH_2Ar), 7.05-7.70 (m, 4 H, ArH).

Anal. Calcd. for $C_{13}H_{17}ClO_3$: C, 60.82; H, 6.63; Cl, 13.84.
Found: C, 60.65; H, 6.80; Cl, 14.03.

4-Benzyloxy-2-butanones (1).- The crude acetal 5 was dissolved in a mixture of dioxane (10 ml) and water (10 ml) with a few milligrams of oxalic acid, and stirred at room temperature until the reaction was shown to be complete by tlc. The solution was extracted with ether (4 x 25 ml) and the combined extracts were washed with saturated sodium hydrogen carbonate (1 x 25 ml), dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residual crude ketone 1 was applied to a silica gel column and the column was eluted with ether/petroleum ether (bp 45-65°). The yields of isolated products are based on alcohol 4.

1a, liquid (85% yield); IR (neat): 1715 cm^{-1} (C=O); NMR (CCl_4): δ 1.98 (s, 3 H, CH_3), 2.52 (t, 2 H, J = 6.8 Hz, CH_2), 3.60 (t, 2 H, J = 6.8 Hz, CH_2O), 4.34 (s, 2 H, CH_2Ar), 7.24 (s, 5 H, ArH).

1b, liquid (79% yield); IR (neat): 1710 cm^{-1} (C=O); NMR (CCl_4):

δ 2.01 (s, 3 H, CH_3), 2.51 (t, 2 H, J = 6.5 Hz, CH_2), 3.62 (t, 2 H, J = 6.5 Hz, CH_2O), 3.70 (s, 3 H, OCH_3), 4.43 (s, 2 H, CH_2-Ar), 6.60-7.40 (m, 4 H, ArH).

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69.
Found: C, 69.36; H, 7.78.

1c, liquid (81% yield); IR (neat): 1715 cm^{-1} (C=O); NMR (CCl_4); δ 2.0 (s, 3 H, CH_3), 2.51 (t, 2 H, J = 6.4 Hz, CH_2), 3.58 (t, 2 H, J = 6.4 Hz, CH_2O), 3.68 (s, 3 H, OCH_3), 4.36 (s, 2 H, CH_2-Ar), 6.65-7.40 (m, 4 H, ArH).

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69.
Found: C, 69.41; H, 7.53.

1d, liquid (73% yield); IR (neat): 1715 cm^{-1} (C=O); NMR (CCl_4): δ 1.97 (s, 3 H, CH_3), 2.51 (t, 2 H, J = 6.4 Hz, CH_2), 3.57 (t, 2 H, J = 6.4 Hz, CH_2O), 3.64 (s, 3 H, OCH_3), 4.33 (s, 2 H, CH_2-Ar), 6.76 (d, 2 H, J = 8.8 Hz), 7.17 (d, 2 H, J = 8.8 Hz, ArH).

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69.
Found: C, 69.05; H, 7.52.

1e, liquid (75% yield); IR (neat): 1710 cm^{-1} (C=O); NMR (CCl_4): δ 2.03 (s, 3 H, CH_3), 2.52 (t, 2 H, J = 6.5 Hz, CH_2), 3.62 (t, 2 H, J = 6.5 Hz, CH_2O), 3.73 and 3.75 (2 s, 6 H, OCH_3), 4.41 (s, 2 H, CH_2Ar), 6.60-7.10 (m, 3 H, ArH).

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.55; H, 7.56.
Found: C, 65.71; H, 7.44.

1f, liquid (71% yield); IR (neat): 1705 cm^{-1} (C=O); NMR (CCl_4): δ 2.02 (s, 3 H, CH_3), 2.52 (t, 2 H, J = 6.3 Hz, CH_2), 3.56 (t, 2 H, J = 6.3 Hz, CH_2O), 3.70 and 3.74 (2 s, 6 H, OCH_3), 6.65-6.90 (m, 3 H, ArH).

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.55; H, 7.56.

Found: C. 65.39; H, 7.47.

<u>1g</u>: liquid (81% yield); IR (neat): 1715 cm^{-1} (C=O); NMR (CCl_4): δ 2.07 (s, 3 H, CH_3), 2.59 (t, 2 H, J = 6.3 Hz, CH_2), 3.70 (t, 2 H, J = 6.3 Hz, CH_2O), 4.51 (s, 2 H, CH_2Ar), 7.05-7.65 (m, 4 H, ArH).

<u>Anal</u>. Calcd. for $C_{11}H_{13}ClO_2$: C, 62.12; H, 6.12; Cl, 16.70.

Found: C, 61.97; H, 6.03; Cl, 16.86.

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