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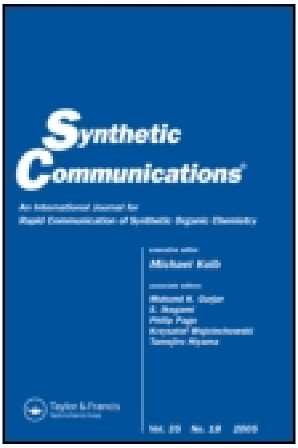

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Accepted author version posted online: 07 Dec 2011.Version of record first published: 26 Mar 2012.

To cite this article: M. Todd Coleman (2012): Use of Diethoxymethane as a Solvent for Phase-Transfer Esterification of Carboxylic Acids, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:13, 1911-1913

To link to this article: http://dx.doi.org/10.1080/00397911.2010.547647

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Synthetic Communications®, 42: 1911–1913, 2012

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.547647

USE OF DIETHOXYMETHANE AS A SOLVENT FOR PHASE-TRANSFER ESTERIFICATION OF CARBOXYLIC ACIDS

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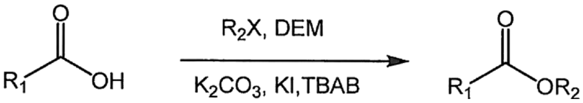
GRAPHICAL ABSTRACT



Abstract *The esterification of carboxylic acids with selected primary alkyl halides in diethoxymethane (DEM) utilizing solid–liquid phase-transfer catalysis has been studied. The use of DEM as the solvent simplifies the process in that a single solvent can be used for both reaction and workup.*

Keywords Diethoxymethane; esterification; phase-transfer catalysis

INTRODUCTION

It has previously been reported that diethoxymethane (DEM) is a good solvent for the *O*-alkylation of phenols using phase-transfer catalysis conditions.[1] The properties of DEM make it a strong candidate for other phase-transfer catalysis reactions. DEM is stable to basic reaction conditions and also has limited water solubility (4.2%), thus eliminating the need for an extraction solvent. Its high boiling point (88 °C) makes it versatile over a wide range of reaction temperatures. The use of DEM as a solvent for the esterification of carboxylic acids using phase-transfer catalysis has been studied and is the subject of this communication.

The classical method used to prepare esters from carboxylic acids is the use of alcohols in the presence of a strong acid catalyst (Fischer esterification). When compounds other than methyl and ethyl esters are desired, alternative routes are sometimes required because of the cost or stability of the alcohol. One alternative method utilizes a phase-transfer catalyst generated in situ from an alkyl halide and an amine in 2-butanone as the solvent. The reactions in this study were carried out in a Parr reactor under pressure.[2] Dichloromethane is also a popular solvent for esterification as has been reported for the preparation of glycidate esters and benzyl benzoate.[3] A

Received November 30, 2010.
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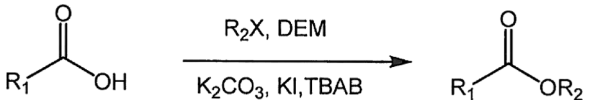
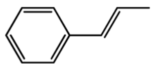
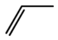
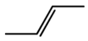
method to prepare substituted benzyl phenylacetate esters, key intermediates in the synthesis of cephalosporin and oxa-β-lactam antibiotics, under solid–liquid phase transfer conditions has also been reported.[4] Key elements of this patented process are the use of a solvent that does not dissolve the carboxylate salt while dissolving the alkyl halide. Solvents utilized were ketones, esters, or nitriles, with acetone being the preferred solvent. The workup described in this reference requires the removal of the initial solvent followed by use of an extraction solvent. These conditions have thus been modified to determine if DEM is suitable for solid–liquid phase-transfer catalyzed reactions.

ESTERIFICATION OF CARBOXYLIC ACIDS

The esterification of various carboxylic acids has been evaluated in DEM using several primary alkyl halides under solid–liquid phase-transfer catalysis (Table 1). The general procedure consists of dissolving the carboxylic acid (0.1 mol) in DEM (150 mL). Potassium carbonate (9.2 g, 0.067 mol), potassium iodide (4.2 g, 0.025 mol), tetrabutylammonium bromide (0.2 g, 0.0006 mol), and the alkyl halide (0.11 mol) were added. The slurry was heated to reflux (80–85 °C) and held for 6 h. After cooling to <50 °C, the mass was diluted with water (100 mL) to dissolve salts, and the layers were separated. The top organic phase was washed with a saturated $NaHCO_3$ solution (50 mL) followed by a saturated NaCl solution (50 mL). After drying over Na_2SO_4 and concentration by rotary evaporation, the crude product was purified by short-path distillation and analyzed by NMR.

Table 1. Esterification of acids using DEM as solid–liquid phase-transfer catalysis reaction solvent



Entry	R_1	R_2	X	Yield
1	Benzyl	Benzyl	Cl	81
2	Phenyl	Benzyl	Cl	78
3	Cyclohexyl	Benzyl	Cl	82
4	Benzyl	Butyl	Br	82
5	Cyclohexyl	Butyl	Br	73
6	Benzyl	Allyl	Cl	30
7	Cyclohexyl	Allyl	Cl	18
8	C_7H_{15}	Benzyl	Cl	89
9	C_7H_{15}	Butyl	Br	72
10		Benzyl	Cl	57
12		Benzyl	Cl	31
11		Benzyl	Cl	82

Yields were generally good for all cases studied. Esterification of unsaturated acids did not result in yields as good as aromatic or saturated acids, with acrylic acid and cinnamic acid resulting in poor yields. Crotonic acid, however, provided a yield similar to the aromatic and saturated acids. Use of allyl chloride as the electrophile resulted in poor yield of allyl esters. It was suspected that the reduced product yield could be due to the low boiling point of allyl chloride. However, a lower reaction temperature did not result in an improvement in yield.

DEM did provide an advantage in product isolation. Because DEM has low solubility in water, an extraction solvent was not required. Isolation involved merely adding water to dissolve salts, decantation, and distillation of the DEM to give crude products, which were purified by short-path distillation.

CONCLUSION

DEM has been demonstrated to be an excellent solvent for the esterification of carboxylic acids using solid–liquid phase-transfer catalysis. Yields are generally good and product workup is greatly simplified. The evaluation of DEM as a solvent for other types of phase-transfer catalysis reactions is being further evaluated in these laboratories.

ACKNOWLEDGMENTS

The author thanks Louise Sandefur, Dimmick Bymaster, and Tim Oster for helpful comments on this manuscript. The author also thanks the FutureFuel Chemical Company Analytical Department for NMR and GC support.

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