Tetrahedron Letters No. 31, pp 2757 - 2760.
© Pergamon Press Ltd. 1978. Printed in Great Britain.

0040-4039/78/0729-2757$02.00/0

TRIPHASE CATALYSIS. INSOLUBILIZED HEXAMETHYLPHOSPHORAMIDE AS A SOLID SOLVENT[1]

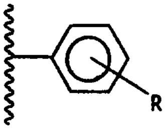
Steven L. Regen,* Alok Nigam, Jacques J. Besse

Department of Chemistry, Marquette University
Milwaukee, Wisconsin 53233

(Received in USA 4 May 1978; received in UK for publication 1 June 1978)

Hexamethylphosphoramide (HMPA) is an extremely effective polar aprotic solvent for promoting nucleophilic displacement and carbanion forming reactions.[2] Use of this solvent, however, has been restricted due to its (1) carcinogenic properties, (2) difficult removal from product mixtures and (3) cost. We have recently begun a program aimed at developing resins which behave like cosolvents.[3] The unique properties of HMPA coupled with its practical limitations make the preparation of solid phase analogs most desirable. Moreover, it seemed possible to us that such materials might exhibit novel and potentially useful catalytic properties. We and others have previously demonstrated that certain polymers can catalyze reaction between substances located in aqueous and organic phases.[4] Such liquid/solid/liquid -- triphase catalytic systems provide a useful alternative to liquid/liquid phase-transfer catalysis. Recently there has been growing interest in solid/liquid phase-transfer catalysis in which the aqueous phase is replaced by solid inorganic salts.[5] This modification eliminates the possibility of water of hydration being co-extracted with ion pairs into the organic phase and thus avoids potential hydrolysis pathways. We reasoned that insolubilized forms of HMPA might impart increased nucleophilicity to crown ether-solubilized salts and thereby act as an additional catalyst for solid/liquid phase-transfer systems; i.e., we envisioned solid/liquid/solid -- triphase catalysis. In addition, it seemed likely that solid phase analogs of HMPA would exhibit significant catalytic activity in liquid/solid/liquid transformations. We now wish to report the preparation of polystyrene-bound HMPA resins[6] and to provide data which demonstrate their ability to catalyze certain nucleophilic displacement reactions conducted both as solid/liquid/solid and liquid/solid/liquid systems.

Resins 1 and 2 were prepared by covalently attaching pentamethylphosphoramide to cross-linked polystyrene by reacting its sodium salt with a chloromethylated form of the copolymer.[7]



functionalized polystyrene--1% divinylbenzene (200-400 mesh)

1, R = $CH_2NCH_3PO[N(CH_3)_2]_2$ (92% ring substitution)

2, R = $CH_2NCH_3PO[N(CH_3)_2]_2$ (17% ring substitution)

Solid/Liquid/Solid -- Triphase Catalysis. An 8-ml culture tube was charged with 0.076 g (0.6 mmol) of benzyl chloride, 1.5 ml of toluene, 0.1 g (1.5 mmol) of potassium cyanide, 0.05 g (0.18 mmol) of 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6) and 0.1 g of resin 1. The tube was sealed with a Teflon-lined screw cap and placed in an oil bath maintained at 80° for 21 h. Analysis of the liquid phase by GLC indicated a 78% yield of benzyl cyanide. In the absence of 1, a similar reaction afforded only 20% of the nitrile.[8] Further examples of solid/liquid/solid triphase catalytic systems are presented in Table I.

Liquid/Solid/Liquid -- Triphase Catalysis. Resin 1 was also found to exhibit significant triphase catalytic activity in liquid/solid/liquid systems. Procedures used here were similar to those previously described (Table I).[4]

Several factors which should be important in determining the efficiency of solid/liquid/solid triphase catalysis are: (1) The rate of solubilization of the organic-insoluble reagent, (2) The relative rate of displacement in the bulk solution vs. at the polymer surface,[9] (3) The partitioning of the nucleophilic reagent between the liquid and solid phases present and (4) The location at which the new salt formed from the displacement is deposited. Although these factors await detailed analysis, our results presented here demonstrate that this technique can be a useful complement to solid/liquid phase-transfer catalysis. Furthermore, we have shown that polystyrene-bound HMPA has considerable potential as a triphase catalyst for liquid/solid/liquid reactions.

Table I

Solid/Liquid/Solid and Liquid/Solid/Liquid Triphase Catalysis

Triphase Method	Reactant	Product	Catalyst(s)[a]	Temp °C	Time h	Yield[b] %
S/L/S[c]	Benzyl Chloride	Benzyl Cyanide	CE	80	21	20
			CE + **1**			78
	Benzyl Bromide	Benzyl Chloride	CE	100	185	14
			CE + **1**			55
			CE + **2**			30
	1-Bromooctane	1-Chlorooctane	CE	110	150	8
			CE + **1**			35
			CE + **2**			21
L/S/L[d]	Benzyl Chloride	Benzyl Cyanide	None	75	45	1
			1			75
			2			34
	1-Bromooctane	1-Chlorooctane	None			0
			1			83
			2			8
		1-Cyanooctane	None	100	92	0
			1			100
			2			36
	1-Bromoadamantane[e]	1-Adamantanol	None	110	10	8
			1			57
			2			88

---

[a] The crown ether (CE) used in all experiments was 18-crown-6. [b] Yields based on starting organic halide were determined by GLC using internal standard techniques. Mass balance in all cases was >97% and reproducibility was excellent. No effort was made to carry out these reactions to completion. [c] Reactions were carried out using 0.05 g (0.18 mmol) of CE, 0.6 mmol of organic halide, 1.5 mmol of KCN or KCl and 0.1 g of resin (when employed) in 1.5 ml of toluene. [d] Reactions were conducted using 0.4 mmol of organic halide in 2.5 ml of toluene, 0.1 g of resin (when used) and 2.5 ml of 5.0 *M* NaCl, NaBr, or NaCN. [e] Reaction of 2 ml of 0.01 *M* 1-bromoadamantane with 2 ml of 0.1 *M* NaOH catalyzed by 0.05 g of resin.

References and Notes

(1) Supported by the Division of Basic Energy Sciences of the Department of Energy (Contract EG-77-S-02-4446).

(2) H. Normant, *Angew. Chem. Int. Ed. Engl.*, **6**, 1046 (1967).

(3) S. L. Regen and L. Dulak, *J. Am. Chem. Soc.*, **99**, 623 (1977); S. L. Regen, *ibid.*, **99**, 3838 (1977).

(4) S. L. Regen, *J. Org. Chem*, **42**, 875 (1977) and references cited therein.

(5) E. V. Dehmlow, *Angew. Chem. Int. Ed. Engl.*, **16**, 493 (1977) and references cited therein.

(6) Tomoi *et al.*, have reported a resin similar to **1** and **2**; however, no proof of structure was provided. In addition, the percent ring substitution and procedures used in the polymer preparation were not specified: M. Tomoi, T. Takubo, M. Ikeda, and H. Kakiuchi, *Chem. Lett.*, 473 (1976). We are grateful to Dr. Charles M. Starks for bringing this to our attention.

(7) In a typical preparation, pentamethylphosphoramide (6.4 g, 38.5 mmol) was added to a suspension of sodium hydride (1.1 g, 45.8 mmol) in 45 ml of distilled benzene and the mixture was refluxed under a nitrogen atmosphere for 15 h. The liquid phase was transferred to a dropping funnel *via* syringe and added dropwise to 4.0 g of chloromethylated polystyrene (6.2 mmol of chlorine/g, 92% ring substitution) swelled in 20 ml of benzene. After the mixture was refluxed for 6 h, the resin was collected by filtration, washed successively with tetrahydrofuran and 5:1 tetrahydrofuran--water, extracted (Soxhlet) with tetrahydrofuran for 48 h under nitrogen and dried under vacuum (24 h, 110° (0.05 mm)) yielding 7.0 g (98%) of resin **1**. Chlorine analysis indicated complete replacement of chloride ion by the phosphoramide (*Anal*. calcd: P, 10.56; N, 14.31. found: P, 10.93; N, 13.67). Resin **2** was prepared using similar procedures.

(8) These experiments were conducted as unstirred systems. We have also carried out similar reactions where stirring (Teflon-coated magnetic stirring bar) was employed and have found increased rates for both the solid/liquid/solid and solid/liquid systems. With stirring, the triphase rate remained significantly greater than that observed for the biphase reaction.

(9) Whether the crown ether remains associated with the nucleophilic reagent at the polymer surface and takes part in the displacement reaction or whether it merely serves to shuttle the reagent to HMPA sites along the polymer remains to be established.