17. Shun'ichi Yamada, Ichiro Chibata, and Ryoya Tsurui: Application of Ion Exchangers in Organic Reactions. IV[1]. Application to the Syntheses of Oximes and Aldehyde Diacetates*.

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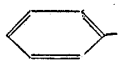
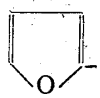
With the remarkable progress of commercial ion exchangers in recent years, many chemical reactions employing ion exchange resins have been found to be of interest. In this paper, the results of the application of ion exchangers for the synthesis of aldehyde diacetates and the preparation of oximes are presented.

As catalytic agents for the synthesis of aldehyde diacetate from aldehyde and acetic anhydride, mineral acids, stannous chloride, zinc chloride, phosphorus trichloride, and recently boron trifluoride have been employed. Instead of these conventional condensing agents, the use of cation exchangers for the reaction gave quite satisfactory results. That is, when the aldehydes such as benzaldehyde, formaldehyde (paraformaldehyde), and furfural were heated with acetic anhydride in the presence of cation exchangers, conversion to the corresponding diacetates readily took place and in good yield. So far as our experiments were concerned the only exception was β-methylmercaptopropionaldehyde whose conversion to the diacetate was less satisfactory than when employing sulfuric acid.

The cation exchangers employed for this study were hydrogen form of strongly acidic resins, such as Amberlite IR-120 and Dowex-50, which were prepared for use as described in our previons paper[2]. The weakly acidic resin Amberlite IRC-50 was also investigated in the synthesis of benzal diacetate, but the resin was ineffective under the conditions employed in our study. The results obtained are listed in Table I.

Table I.

Synthesis of Aldehyde Diacetate, $RCH(OCOCH_3)_2$

R	Cation Exchanger	Yield (%)
	Dowex-50	92.0 (72.0)
	Amberlite IRC-50	0
H-	Amberlite IR-120	62.9
$CH_3SCH_2CH_2$-	Dowex-50	46.6
	Amberlite IR-120	74.8
	Dowex-50	81.6

The advantages of this method are that the same catalyst can be used repeatedly, separation problems are simplified as the cation exchangers are substantially insoluble in the reactants, so that the troublesome procedures inherent to conventional catalysts such as neutralization, removal of catalyst, and purification are eliminated, and sensitive molecules can, in some cases, be made to react without polymerization or other side reactions occurring, e.g. furfural was converted successfully to the diacetate by cation exchangers.

The preparation of oximes by the use of anion exchangers was also studied. The

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1) S. Yamada, I. Chibata, R. Tsurui: This Bulletin, 2, 59 (1954).
2) This Bulletin, 1, 14 (1953).

synthesis of oximes such as aldoxime and ketoxime from carbonyl derivatives and hydroxylamine are frequently employed in organic chemistry. The usual method is that the carbonyl compounds are made to react with hydroxylamine hydrochloride or sulfate by adding an acid removing agent such as sodium bicarbonate, sodium acetate, etc. In this method, as the oximes produced are more or less contaminated with inorganic impurities, the purification process such as extraction, distillation, and recrystallization is necessary. This method is simplified by the use of anion exchangers instead of above-mentioned inorganic substances.

The effective ion exchangers studied in this reaction were the weakly basic anion exchange resin, Amberlite IR-4B, and the strongly basic anion exchange resin, Amberlite IRA-400, but the former is recommended because of its larger exchange capacity. The solvents used in this study were water and aqueous alcohol. By this method oximes of cyclohexanone, butyraldehyde, and benzophenone were prepared. Results are shown in Table II.

Table II.

Preparation of Oximes

Oxime	Anion Exchanger	Yield (%)
Cyclohexanone oxime	Amberlite IR-4B	70.3
	Amberlite IRA-400	74.6
Butyraldoxime	Amberlite IR-4B	80.5
Benzophenone oxime	Amberlite IR-4B	quant.
3,4-Dimethyl-5-aminoisoxazole	Amberlite IR-4B	90.0

Furthermore, this method was extended to the synthesis of 3,4-dimethyl-5-aminoisoxazole, the starting material for the synthesis of sulfisoxazole. It is known from the patent of Hoffman-La Roche[3] which lets α-acetopropionitrile react with hydroxylamine hydrochloride in the presence of potassium acetate that this reaction proceeds through oxime and further cyclization yields isoxazole compound. When anion exchange resin, Amberlite IR-4B, was substituted for potassium acetate in this reaction, the desired product 3,4-dimethyl-5-aminoisoxazole was obtained without any difficulty in such a good yield as 90% of the theoretical.

Needless to say, the used resins can be regenerated and used repeatedly and the oximes obtained in this method are not contaminated with inorganic substances.

These results show that the use of ion exchangers as acid removing agent is practical, convenient, and simplifies the procedure of the preparation of oximes.

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Experimental

Benzal Diacetate—To an agitated mixture of acetic anhydride (11 g.) and Dowex-50 (1 g.), was added dropwise benzaldehyde (10 g.) over a period of ten minutes. After stirring one hour at 60° and several hours longer while the reaction mixture cooled to room temperature, the resins were filtered off. The filtrate was then poured into ice water, the separated colorless crystals were collected, and washed with water. After drying, 18 g. (92%) of the diacetate, m.p. 45~46°, was obtained. *Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.42; H, 5.40. In the same reaction, the filtrate of the reaction mixture was taken up in ether and washed with sodium hydroxide solution, then with water, and dried over anhydrous sodium sulfate. The solvent was removed and the residue distilled *in vacuo* yielding 72% of the product, $b.p_{20}$ 154°.

Methylene Diacetate—A mixture of paraformaldehyde (5 g.), acetic anhydride (20 g.), and Amberlite IR-120 (2 g.) was refluxed while stirring for 30 minutes. During the reaction, the insoluble paraformaldehyde gradually disappeared and a clear solution resulted. After removing the resin

3) Hoffman-La Roche: U.S. Pat. 2,430,094; Brit. Pat. 595,775.

by filtration, the reaction mixture was taken up in ether. The ether solution was washed with water, dried, and distilled *in vacuo*, to yield 15.9 g. (62.9%), b.$p_{11\sim12}$ 62~65°. *Anal.* Calcd. for $C_5H_8O_4$: C, 45.45; H, 6.10. Found: C, 45.81; H, 5.72.

β-Methylmercaptopropionaldehyde Diacetate—β-Methylmercaptopropionaldehyde (5.2 g.), acetic anhydride (7.6 g.), and Dowex-50 (0.8 g.) were mixed and heated while stirring at 90° for 3 hours. After completion of the reaction, the resins were removed by filtration. The filtrate was extracted with ether, and the ethereal solution was washed with water, and dried over anhydrous sulfate. The solvent was removed and the residue distilled *in vacuo* yielding 4.8 g. (46.6%) of colorless oil, b.p_5 119°. *Anal.* Cald. for $C_8H_{14}O_4S$: C, 46.60; H, 6.84. Found: C, 46.12; H, 6.61.

Furfural Diacetate—A mixture of furfural (10 g.), acetic anhydride (25 g.), and Dowex-50 (1 g.) was heated while stirring at 80~90° for 4 hours. The reaction mixture was filtered to remove the resins. On fractional distillation of the filtrate, after some forerunner of acetic anhydride, the main fraction came over at 142~144° (20 mm.), 16.8 g. (81.6%), which soon solidified on standing.

In the same reaction using Amberlite IR-120, the filtrate of the reaction mixture poured into ice water yielded plates of m.p. 52~53°, 7.6 g. (74.8%). *Anal.* Calcd. for $C_9H_{10}O_5$: C, 54.54; H, 5.09. Found: C, 54.02; H, 4.88.

Cyclohexanone Oxime—Amberlite IR-4B (14 g.) was added to a solution of cyclohexanone (5 g.) and hydroxylamine hydrochloride (5 g.) in 65% aqueous alcohol (40 cc.). The reaction mixture was kept at 50° for several hours while stirring. At the end of the time, the resins were filtered and washed with hot alcohol. Concentration of the combined filtrate and washings gave colorless prisms, m.p. 86~89°, not depressed by mixing with an authentic specimen.

The use of Amberlite IRA-400 in this reaction gave the oxime in 74.6% yield.

Butyraldoxime—To an agitated mixture of Amberlite IR-4B (14 g.) and hydroxylamine hydrochloride (8 g.) in methyl alcohol (50 cc.) and water (4 cc.) was added dropwise butyraldehyde (7.2 g.), the temperature rising to 40°. Stirring was continued for additional 2 hours at room temperature, and then the resins were filtered off and washed with methyl alcohol. Removal of the solvent from the combined filtrate and washings, and distillation *in vacuo* yielded 7 g. (80.5 %) of colorless oil, b.$p_{16\cdot5}$ 67°. *Anal.* Calcd. for C_4H_9ON: N, 16.08. Found: N, 15.73.

Benzophenone Oxime—A solution of hydroxylamine hydrochloride (5.5 g.) dissolved in aqueous alcohol was added dropwise to an agitated mixture of benzophenone in alcohol (30 cc.) and Amberlite IR-4B (9.5 g.), whereupon the temperature rose to 40°. Then the reaction mixture was heated under reflux for 10 minutes, and the resins were filtered hot and washed with a small amount of alcohol. On cooling the alcoholic solution, colorless crystals, m.p. 140~143°, separated. An additional product isolated from the filtrate by concentration afforded an almost quantitative yield. *Anal.* Calcd. for $C_{13}H_{11}ON$: N, 7.10. Found: N, 7.08.

3,4-Dimethyl-5-aminoisoxazole—To an agitated mixture of Amberlite IR-4B (20 cc.) and hydroxylamine hydrochloride (3.4 g.) in 20 cc. water, α-acetopropionitrile (3.2 g.) was added dropwise over a period of 15 minutes at room temperature. Stirring was continued for 2 hours at 50°. The resins were removed from the hot reaction mixture by filtration and washed with hot water. Concentration of the filtrate yielded 3.2 g. (90.0%) of colorless prisms, m.p. 120~123°. A mixed melting point determination with an authentic sample showed no depression.

Summary

For the synthesis of aldehyde diacetate from aldehyde and acetic anhydride, cation exchange resins were found to be an effective and convenient catalyst. The authors also simplified the method of oxime preparation by employing anion exchange resins as acid removing agent.

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