

obtained starting from Fmoc-L-Phe-Cl and also when the coupling of either the D or L isomer was carried out by the two-phase method (CH_2Cl_2 - NaHCO_3 - H_2O) with H-Phe-OCMe₃, H-Phe-OMe, or H-Ala-OMe. See table I for characterization data.

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Registry No. Z-Phe-Phe-OCH₃, 111524-81-3; Z-D-Phe-Phe-OCH₃, 81819-48-9; Z-Phe-Phe-OC(CH₃)₃, 111524-82-4; Z-D-Phe-Phe-OC(CH₃)₃, 111524-83-5; Ts-Phe-Ala-OCH₃, 111524-84-6; Ts-D-Phe-Ala-OCH₃, 111524-85-7; Fmoc-Phe-Phe-OCH₃, 111524-86-8; Fmoc-D-Phe-Phe-OCH₃, 111524-87-9; BOC-Phe-Phe-OCH₃, 111524-88-0; BOC-D-Phe-Phe-OCH₃, 94778-64-0; Bz-Phe-Ala-OCH₃, 111524-89-1; Bz-D-Phe-Ala-OCH₃, 111524-90-4; H-Phe-Phe-OCH₃-CF₃COOH, 111524-92-6; H-D-Phe-Phe-OCH₃-CF₃COOH, 111524-94-8; Fmoc-Phe-OH, 102410-65-1; Fmoc-D-Phe-OH, 111524-95-9; Fmoc-Phe-Cl, 111524-96-0; Fmoc-D-Phe-Cl, 111524-97-1; Ts-Phe-OH, 111524-98-2; Ts-Phe-Cl, 111524-99-3; Ts-D-Phe-OH, 60712-47-2; Ts-D-Phe-Cl, 63406-97-3; H-Phe-OCH₃-HCl, 7524-50-7; H-Phe-Phe-OCH₃, 111524-91-5.

A Simple, Efficient, and Highly Selective Method for the Regeneration of Carbonyl Compounds from Oximes and Semicarbazones

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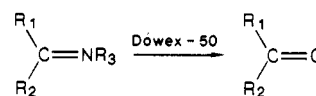
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Regeneration of carbonyl compounds from their oximes, semicarbazones, and other derivatives under mild conditions has recently^{1a-e,2a} received much attention. Classically, it involved hydrolytic cleavage by exchange³ under acidic conditions (phthalic anhydride-water,^{3a} H^+ /pyruvic

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Scheme 1^a



^a R_1 = alkyl; R_2 = alkyl or H; R_3 = OH, or NHCONH_2 .

Table I. Cleavage of Oximes and Semicarbazones with Dowex-50

entry	regenerated carbonyl compounds ^a	refluxing time (h)	yield (%) ^b
1	cyclohexanone	2	87 ^c 90 ^d
2	acetophenone	1	90 ^c 96 ^d
3	indanone	2	85 ^c 91 ^d
4	benzophenone	3	85 ^c 90 ^d
5	benzaldehyde	5	32 ^c 20 ^d
6	<i>m</i> -methoxybenzaldehyde	5	30 ^c 26 ^d
7	citral	8	no reactn
8	ethyl 2-oxacyclohexanecarboxylate	3	74 ^c 76 ^d
9	ethyl 2-oxacyclopentanecarboxylate	3	75 ^c 78 ^d
10	4-carbethoxy-3-methyl-2-cyclohexen-1-one (Hagemann's ester)	3	80 ^c 85 ^d

^a The regenerated carbonyl compounds are compared with the authentic samples (TLC, IR, NMR). ^b Yield refers to isolated products. ^c Carbonyl compounds obtained from oximes. ^d Carbonyl compounds obtained from semicarbazones.

acid,^{3b,c} aqueous oxalic acid,^{3d} nitrous acid,^{3e} levulinic acid-aqueous hydrochloric acid,^{3f} hydrochloric acid-formaldehyde,^{3g} aqueous acetic acid,^{3h} sodium hydrogen sulfite³ⁱ). Since these methods exclude acid-sensitive ketones and aldehydes, a variety of oxidative¹ (cetyltrimethylammonium permanganate (CTAP),^{1a} (diacetoxyiodo)benzene,^{1b} chromyl chloride,^{1c} potassium bromate,^{1d} dinitrogen tetroxide,^{1e} pyridinium chlorochromate,^{1f} chromium(VI) oxide in the form of Jones and Collins reagent,^{1g} lead(IV) acetate,^{1h} ozone,¹ⁱ cerium(IV) ammonium nitrate,^{1j} nitrosochloride-pyridine,^{1k} nitronium and nitronium salts,^{1l} Barton's reagent,^{1m} bromine,¹ⁿ alkaline hydrogen peroxide,^{1o} periodic acid,^{1g} bis(pyridinesilver) permanganate,^{1p} bis(triphenylphosphine)palladium/oxygen,^{1q} sodium nitrite,^{1r} thallium(III) nitrate,^{1s} thallium(III) acetate^{1t}) and reductive² (pentacarbonyl iron,^{2a-c} aluminum triisopropoxide,^{2d} titanium(III) chloride,^{2e} chromium(II) acetate,^{2f} zinc-acetic acid,^{2g} Raney nickel alloy in alkaline solution (nascent hydrogen)^{2h}) procedures have been developed over the years. These methods, though satisfactory for simple molecules, often are less useful for complex molecules because of (a) oxidation or reduction of other easily oxidizable or reducible groups present in the molecule and (b) overoxidation or overreduction of the lib-

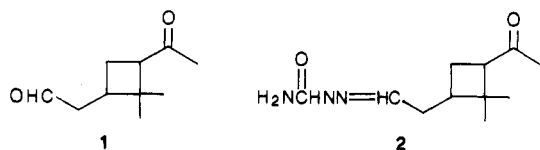
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erated ketones and aldehydes. Often, these reagents are toxic⁴ and expensive. Thus, the literature still demands a reagent that would be mild, selective, nonhazardous, and inexpensive.

We describe in this note a simple method for the regeneration of carbonyl compounds from their oximes and semicarbazones (Scheme I) using a cation exchange resin Dowex-50⁵ (Table I).

In a typical reaction, the derivative (oxime or semicarbazone) of the carbonyl compound was heated at reflux with stirring in an aqueous suspension of Dowex-50. At the end of the reaction (monitored by TLC), the reaction mixture was steam-distilled and the product was isolated in a pure state by solvent extraction of the steam-distillate. If the reaction was carried out on a milligram scale, the product could be isolated by direct extraction of the aqueous filtrate of the reaction mixture. Ketones were obtained readily in high yield (Table I, entries 1-4), whereas aldehydes (entries 5, 6) were formed slowly.⁶ However, the remaining oxime or semicarbazone after isolation of the aldehyde could be recycled to raise recovery to a good level. It is noteworthy that the oxime and the semicarbazone of citral remain unaffected under these conditions. Our method is especially good for recovery of β -keto esters (entries 8, 9) and the vinylogous β -keto ester (entry 10), which are, in general, susceptible to decarboxylation in acidic media.

The above results suggest that this procedure will show considerable selectivity for the regeneration of ketones over that of aldehydes. This was established by an experiment in which a mixture of an equal amount of the derivatives (oxime or semicarbazone) of acetophenone and benzaldehyde was treated with Dowex-50 for 1 h under this condition, followed by steam distillation to give a quantitative (90%) recovery of acetophenone with a trace of benzaldehyde.⁷ If the bissemicarbazone (mp 195 °C; IR 1690 cm^{-1}) of the keto aldehyde 1⁸ (IR 2720, 1720, 1700 cm^{-1}) was treated with Dowex-50 for 1 h under identical conditions, the extract of the aqueous filtrate of the reaction mixture gave the monosemicarbazone 2 (IR 1700, 1690 cm^{-1} , absence of 2720 and 1720 cm^{-1} peaks) as a semisolid mass in low yield.⁹ This technique of selective deblocking of a ketone in the presence of an aldehyde can serve as an alternative to the Luche reaction.¹⁰



In conclusion, the methodology described here for the regeneration of carbonyl compounds from their oximes and semicarbazones with Dowex-50 is manipulatively simple, mild, highly selective, and economical¹¹ and it avoids

(4) Luckey, T. D.; Venugopal, B.; Hutcheson, D. *Heavy Metal Toxicity, Safety and Hormology*; Academic Press, New York, 1975.

(5) Dowex-50 used was manufactured by Fluka A. G., Switzerland. The commercial Dowex-50 was soaked in 4 N HCl overnight and then washed with distilled water until acid-free (tested with AgNO_3 solution) and used in moist form.

(6) The yield of aldehyde did not change even after prolonged heating or with a larger quantity of Dowex-50. The rest of the material other than aldehyde is starting oxime or semicarbazone.

(7) The ratio of acetophenone and benzaldehyde is found to be ~93:7 by ^1H NMR integration.

(8) Conia, J. M.; Faget, C. *Bull. Soc. Chim. Fr.* 1964, 1963.

(9) No attempt has been made for optimization of yield.

(10) Luche, J. L.; Gemal, A. L. *J. Am. Chem. Soc.* 1979, 101, 5848.

(11) The used Dowex-50 after being washed with methanol and water can be recycled after regeneration.⁵

disadvantages of other methods.

Experimental Section

Melting points were taken in an electrical bath (Gallenkamp, England) and are uncorrected. For comparison, IR spectra were recorded on a Perkin-Elmer Model 298 spectrometer and ^1H NMR spectra were recorded on a T60A spectrometer of Varian Associates in CCl_4 or CDCl_3 solutions with Me_4Si as internal standard. Thin layer chromatography was done on precoated silica gel plates (Eastman Kodak Co.). Oxime and semicarbazones were prepared by standard methods.¹²

General Procedure for the Regeneration of Carbonyl Compounds from Oximes and Semicarbazones. The oxime or the semicarbazone (5 mmol) was heated at reflux (bath temperature 120 °C) with stirring in an aqueous (25 mL) suspension of regenerated⁵ Dowex-50 (50% of the derivative by weight) for 1-5 h (Table I). The reaction mixture was steam-distilled.¹³ The distillate was saturated with sodium chloride and was extracted with ether (3 \times 25 mL). The ether extract was dried (Na_2SO_4) and was evaporated to give the pure carbonyl compound which was identified by comparison with an authentic sample (TLC, IR, and ^1H NMR).

Regeneration of Acetophenone and Benzaldehyde from a Mixture of Their Semicarbazones and Oximes. Acetophenone semicarbazone (532 mg, 3 mmol) and benzaldehyde semicarbazone (490 mg, 3 mmol) were heated with Dowex-50 (500 mg) in aqueous suspensions under identical conditions as above for 1 h. After steam distillation, the distillate was extracted (ether) to give a colorless oil (355 mg) which was found to be a 93:7 mixture of acetophenone (recovery 90%) and benzaldehyde by ^1H NMR analysis.

The mixture of oximes under identical conditions produced an almost identical result (acetophenone/benzaldehyde 94:6).

Preparation of Monosemicarbazone 2. The bissemicarbazone of 1 (1.1 g, 4 mmol) was heated at reflux with Dowex-50 (500 mg) in a similar way as above for 1 h. The reaction mixture was cooled to room temperature and was filtered. The filtrate was saturated with sodium chloride and was extracted with ether (3 \times 30 mL). The ether extract was dried (Na_2SO_4) and was evaporated to leave a semisolid mass (265 mg, 30%), which was identified as the monosemicarbazone 2: IR (CHCl_3) 1700, 1690 cm^{-1} (absence of CHO peaks at 2700 and 1720 cm^{-1}).

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Registry No. 1 (bissemicarbazone), 6611-90-1; 2, 111904-15-5; Dowex-50, 12640-54-9; PhAc, 98-86-2; Ph_2CO , 119-61-9; PhCHO, 100-52-7; *m*- $\text{MeOC}_6\text{H}_4\text{CHO}$, 591-31-1; $\text{PhC}(\text{Me})=\text{NOH}$, 613-91-2; $\text{PhC}(\text{Me})=\text{NNHCONH}_2$, 2492-30-0; $\text{Ph}_2\text{C}(\text{=NOH})$, 574-66-3; $\text{Ph}_2\text{C}(\text{=NNHCONH}_2)$, 14066-73-0; $\text{PhCH}=\text{NOH}$, 932-90-1; $\text{PhCH}=\text{NNHCONH}_2$, 1574-10-3; *m*- $\text{MeOC}_6\text{H}_4\text{CH}=\text{NOH}$, 38489-80-4; *m*- $\text{MeOC}_6\text{H}_4\text{CH}=\text{NNHCONH}_2$, 14066-64-9; cyclohexanone, 108-94-1; indanone, 30286-23-8; citral, 5392-40-5; ethyl 2-oxocyclohexanecarboxylate, 1655-07-8; ethyl 2-oxocyclopentanecarboxylate, 611-10-9; cyclohexanone oxime, 100-64-1; cyclohexanone semicarbazone, 1589-61-3; indanone oxime, 111904-16-6; indanone semicarbazone, 111904-17-7; ethyl 2-oxocyclohexanecarboxylate oxime, 111904-12-2; ethyl 2-oxocyclohexanecarboxylate semicarbazone, 111904-13-3; ethyl 2-oxocyclopentanecarboxylate oxime, 4492-46-0; ethyl 2-oxocyclopentanecarboxylate semicarbazone, 16689-52-4; 4-carbethoxy-3-methyl-2-cyclohexen-1-one, 487-51-4; 4-carbethoxy-3-methyl-2-cyclohexen-1-one oxime, 111933-48-3; 4-carbethoxy-3-methyl-2-cyclohexen-1-one semicarbazone, 111904-14-4.

(12) Vogel, A. I. A. *Textbook of Practical Organic Chemistry*, 3rd ed.; English Language Book Society and Longman Group Limited: London, 1973.

(13) In the case of β -keto esters (entries 8, 9, 10), a fresh batch of Dowex-50 was added before steam distillation for completion of reaction and better recovery.