Table I

Starting benzaldehyde	Registry no.	Isoquinoline	Registry no.	Pomeranz–Fritsch vs. oxazole: Total mixed, %	Pomeranz–Fritsch vs. oxazole: Oxazole/ isoquinoline	Registry no. of oxazole
o-Methyl	529-20-4	8-Methyl[5]	62882-00-2	18	3/97	62882-03-5
p-Methyl	104-87-0	6-Methyl[5]	42398-73-2	21	6/94	62882-04-6
m-Methyl	620-23-5	5- + 7-Methyl	62882-01-3 (5) 54004-38-5 (7)	22	6/94	62882-05-7
o-Chloro	89-98-5	8-Chloro[6]	34784-07-1	9	36/64	62881-98-5
p-Chloro	104-88-1	6-Chloro	62882-02-4	25–50	61/39	46047-24-9
m-Chloro	587-04-2	5- + 7-Chloro[7]	5430-45-5 (5) 34784-06-0 (7)	14	23/77	62882-06-8
o-Nitro	552-89-6			All oxazole[2]		62882-07-9
m-Nitro	99-61-6			All oxazole		35582-07-1
p-Nitro	555-16-8			All oxazole[6]		62882-08-0

Anal. Calcd for $C_9H_8N_2O$: C, 67.50; H, 5.00. Found: C, 67.49; H, 5.10.

2-(*x*-Chlorophenyl)oxazoles. The three aminophenyloxazoles (3-g samples) were subjected to Sandmeyer reactions.[4] 2-(*m*-Chlorophenyl)oxazole (mp 34–35 °C) was obtained after recrystallization from methylcyclohexane. The yield of crude compound before recrystallization was 3 g (90% of the theoretical).

Anal. Calcd for C_9H_6NOCl: C, 60.17; H, 3.34. Found: C, 60.05; H, 3.25.

2-(*p*-Chlorophenyl)oxazole, mp 80–81 °C after recrystallization. The crude product weighed 3.2 g (93% of the theoretical).

Anal. Calcd for C_9H_6NOCl: C, 60.17; H, 3.34. Found: C, 60.25; H, 3.30.

2-(*o*-Chlorophenyl)oxazole was a liquid, bp 130 °C (7.5 mm), picrate mp 114–115 °C. There was obtained 3 g (90% of the theoretical). The chlorophenyloxazoles were compared with those prepared by the Pomeranz–Fritsch reactions.

Anal. Calcd for C_9H_6NOCl: C, 60.17; H, 3.34. Found: C, 60.30; H, 3.10.

Pomeranz–Fritsch Reactions with Chloro Substituents. Pomeranz–Fritsch reactions were run on benzal aminoacetals from *o*-,[5,6] *p*-,[5] and *m*-chlorobenzaldehydes.[7]

The yields of chloroisoquinolines obtained were as indicated in the literature. However, the crude products in each case were separated on a Hewlett-Packard 5750 research chromatograph. The temperature was maintained at 240 °C with 30 psi He pressure. An 20-ft column containing 20% Carbowax 20M on Anakrom 50/60 AB was used and peaks were separated in collection tubes and submitted to mass spectrometry. Peaks for the respective aldehyde, its corresponding acid, the oxazole, and chloroisoquinoline were noted but only the oxazole and chloroisoquinoline were compared quantitatively. The yield of oxazole as compared to isoquinoline for *o*-chlorobenzal aminoacetal was 36% oxazole to 64% 8-chloroisoquinoline, for the meta 23% oxazole to 77% 5- and 7-chloroisoquinoline mixture, and for para 61% oxazole to 39% 6-chloroisoquinoline.

A crude dimethyl *p*-chlorobenzalaminoacetal (40 g, from equivalent weights of aldehyde and aminoacetal heated to 120 °C to remove water) was dissolved in 200 mL of concentrated H_2SO_4 at 5 °C, added to 80 g of P_2O_5 and 20 mL of H_2SO_4, and heated to 160 °C for an additional 20 min. The mixture was cooled, neutralized, and steam-distilled. An ether extract of the steam distillate was evaporated to dryness to give 10 g of crude material. This was first extracted with 13% aqueous HCl to remove 6-chloroisoquinoline, then with 38% HCl to remove the oxazole, leaving *p*-chlorobenzaldehyde.

2-(*p*-Chlorophenyl)oxazole. Analysis, see above; mixture melting point was correct.

6-Chloroisoquinoline. Anal. Calcd for C_9H_6NCl: C, 66.06; H, 3.67. Found: C, 66.10; H, 3.70.

Methylisoquinolines by the Pomeranz–Fritsch Reaction. *o*-Methylbenzalaminoacetal and *p*-methylbenzalaminoacetal have been cyclized by Pomeranz[5] to 8-methylisoquinoline and 6-methylisoquinoline, respectively. We have cyclized the *m*-methylbenzalaminoacetal to a mixture of 5- and 7-methylquinolines. *m*-Tolualdehyde and aminoacetaldehyde dimethyl acetal were heated in equivalent amounts to 120 °C until the water was removed. This crude product (50 g) was then dissolved in 250 mL of H_2SO_4 at 5 °C and this mixture added to a mixture of 75 g of P_2O_5 and heated at 160 °C for 25 min.

The reaction product was cooled, neutralized, and steam-distilled. The crude distillate was ether extracted and subjected to gas chromatography. The 5- and 7-methylisoquinoline mixture was extracted with dilute acid and recovered. It was possible to crystallize 6 g of 7-methylisoquinoline, melting at 66 °C from the 10 g of crude product. The yield of 2-(*m*-methylphenyl)oxazole was only 1% in this case.

Registry No.—Dimethyl aminoacetal, 22483-09-6; *m*-nitrobenzal aminoacetal, 62882-09-1; 2-(*o*-aminophenyl)oxazole, 62882-10-4; 2-(*p*-aminophenyl)oxazole, 62882-11-5; 2-(*m*-aminophenyl)oxazole, 35582-08-2; 2-(*o*-chlorophenyl)oxazole picrate, 62881-99-6; dimethyl *o*-chlorobenzalaminoacetal, 62882-12-6; dimethyl *m*-chlorobenzalaminoacetal, 62882-13-7; dimethyl *p*-chlorobenzalaminoacetal, 54879-73-1; dimethyl *o*-methylbenzalaminoacetal, 54879-71-9; dimethyl *p*-methylbenzalaminoacetal, 54879-70-8; dimethyl *m*-methylbenzalaminoacetal, 62882-14-8.

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Conjugate Addition of Grignard Reagents to Ethyl Acrylate

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The homologation of alkyl and aryl halides with a three-carbon chain terminating in a carboxyl or ester function is of some importance in synthesis,[1,2] and a variety of methods can be utilized to accomplish the transformation. Among these methods is the reaction of aryl and heterocyclic iodo compounds with the copper(I) salt of ethyl propiolate,[3] palladium-catalyzed vinylic hydrogen substitution reaction of methyl acrylate with aryl, benzyl, and styryl halides,[4] ethylenation of secondary and tertiary alkyllithiums, followed by carbonation,[5] alkylation of metalated α,β-ynamines with allyl and *n*-alkyl halides, followed by hydrolysis,[6] and conjugate addition of methyl propiolate with organocopper reagents[7] or mixed cuprate reagents.[8] These methods suffer, however, the following disadvantages. Firstly, although some of them give satisfactory yields, none of them has wide applicability, and furthermore, certain reagents, such as 1-propynyl-2,2,6,6-tetramethylpiperidine,[6] are not readily accessible. Secondly, when the product is an unsaturated ester, e.g., $CH_2{=}CHCH_2CH{=}CHCOOCH_3$,[7] subsequent hydrogenation

Table I. Reaction of Grignard Reagents with Ethyl Acrylate

$$RX + Mg \rightarrow RMgX$$

$$RMgX + CH_2{=}CHCOOEt \rightarrow RCH_2CH_2COOEt$$

RX	Registry no.	Temp, °C	RCH_2CH_2COOEt[a]	Registry no.	Bp, °C (mm)	Yield, %[b]
Bromobenzene	108-86-1	−20[c]	$PhCH_2CH_2COOEt$	2021-28-5	85 (2)[d]	54
1-Bromopentane	110-53-2	−40	$CH_3(CH_2)_6COOEt$	106-32-1	99 (40)[e]	80
Vinyl bromide	593-60-2	−35 ~ −40[f]	$CH_2{=}CHCH_2CH_2COOEt$	1968-40-7	55 (40)[g]	41
6-Bromo-1-hexene	2695-47-8	−45 ~ −50	$CH_2{=}CH(CH_2)_6COOEt$	35194-39-9	72 (2)[h]	73
Benzyl chloride	100-44-7	−25[c]	$PhCH_2CH_2CH_2COOEt$	10031-93-3	112 (3.5)[i]	69
Cyclohexyl bromide	108-85-0	−45 ~ −50	Ethyl 3-cyclohexylpropanoate	10094-36-7	72 (2)[j]	68

[a] All products gave satisfactory spectroscopic data. [b] Yields given represent distilled product. [c] Cooling below this temperature will cause the Grignard reagent to solidify. [d] Lit.[15] 123 °C (16 mm). [e] Lit.[16] 104 °C (80 mm). [f] −25 °C at onset of the reaction. [g] Lit.[17] 144–146 °C. [h] Lit.[18] 114–116 °C (15 mm). [i] Lit.[19] 130–131 °C (10 mm). [j] Lit.[20] 105–113 °C (17 mm).

is clearly incompatible with the presence of other unsaturation in the molecule. There has been one report of conjugate addition of lithium di-*sec*-butylcuprate to ethyl acrylate giving ethyl 4-methylhexanoate.[2]

In spite of these methods for the extension of a three-carbon chain, the most obvious approach would be the conjugate addition of Grignard reagents with acrylate esters. However, although the 1,4 additions of Grignard reagents to substituted acrylates, such as crotonate, tiglate, and cinnamate, in the presence of copper catalyst under well-defined reaction conditions generally give good to fair yields,[9,10] *sec*-butyl acrylate itself was reported to give only polymerization material.[11]

We reasoned that the key to effecting 1,4 addition to acrylate lay simply in conducting the reaction at low temperature, thus reducing the extent of polymerization. We therefore examined the reactions of ethyl acrylate with Grignard reagents generated from primary, secondary, aryl, benzylic, and vinyl halides and found that it was indeed the case. For example, when ethyl acrylate in ether was added very slowly to a solution of a threefold excess of pentylmagnesium bromide in ether at −40 °C and a catalytic amount of cuprous chloride[12] was added in 13 portions during the course of the reaction, ethyl octanoate could be isolated in 80% yield.[13] Some of our results are given in Table I.

In summary, we feel that the three-carbon homologation is easy to operate and gives good to fair yields with a variety of halides, and we expect that it will find use in synthesis.

Experimental Section

General Reaction Procedure. Ethyl Octanoate. The solution of pentylmagnesium bromide was prepared from 6 g (0.25 g-atom) of magnesium turnings and 37.75 g (0.25 mol) of 1-bromopentane in 400 mL of ether[14] under a nitrogen atmosphere. The solution was cooled to −40 °C and kept at that temperature throughout the reaction. Cuprous chloride[12] (50 mg) was added and then 8.3 g (0.083 mol) of ethyl acrylate in 250 mL of ether was added dropwise over a 3-h period with vigorous stirring. After each 15-min interval during the addition another 50 mg of cuprous chloride was added. After each addition, the system was evacuated and then filled with nitrogen. The last portion was added just after completion of the addition of ethyl acrylate. A total of 650 mg (2.6 mol % with respect to the Grignard reagent) of cuprous chloride was used. The cooling bath was then removed and the reaction mixture was stirred at ambient temperature for 30 min and at room temperature for 20 min. The dark solution was poured rapidly into a mixture of crushed ice and concentrated hydrochloric acid with vigorous stirring. The aqueous solution was separated and extracted with ether. The combined ether extracts were washed with saturated sodium bicarbonate, water, and with saturated brine, then dried ($MgSO_4$), filtered, and concentrated. The residue was distilled to yield 11.4 g (80%) of pure ethyl octanoate, bp 99 °C (40 mm) [lit.[16] 104 °C (80 mm)]. The product was identified by comparison of its infrared and NMR spectra and its VPC behavior with those of an authentic sample.

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Registry No.—$CH_2{=}CHCOOEt$, 140-88-5.

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Chromium(VI) Oxidations of Secondary Alcohols in the Presence of Amino Groups, or How to Solubilize Chromium(III) in Base

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We wish to report a method for the facile solubilization of Cr(III) in basic water; this method conveniently overcomes serious product isolation difficulties in the oxidation of alcohols containing amino groups.

In connection with another problem, we recently desired to effect transformation of the amino alcohol **1** to the amino ketone **2** (actually expected to exist as the carbinolamine **3** or the enamine **4**).[1] We wished to perform this oxidation under acidic conditions for several reasons: to protect the amino