Table II. NMR Data (δ) for 2-Pyridones

compd	NMR	position 2	3	4	5	6	7	8	9	10	11	12	12a	12b	13	13a	13b	14	phenyl
3b[a]	^{13}C	158.0	141.1	119.0	105.8	141.6	25.2	17.7	20.7	42.1			165.7	52.1		165.7	52.2		
	^{1}H		9.76 (s, 1 H)				2.95 (t, 2 H, J = 6 Hz)	1.83–1.69 (m, 4 H)		4.00 (t, 2 H, J = 6 Hz)				3.75 (s, 3 H)			3.69 (s, 3 H)		
3c[a]	^{13}C	157.9	142.0	117.9	107.2	143.8	28.8	27.0	28.2	28.2	43.8		165.4	52.3		166.3	52.2		
	^{1}H		9.85 (s, 1 H)				2.94 (m, 2 H)	1.65 (m, 6 H)			4.37 (m, 2 H)			3.75 (s, 3 H)			3.69 (s, 3 H)		
4b[b]	^{13}C	167.5	119.3	147.3	110.0	159.3	23.1	18.3	29.6	52.6					169.7			168.6	130–134
	^{1}H		7.40 (s, 1 H)				3.60 (t, 2 H, J = 8 Hz)	2–2.3 (m, 4 H)		4.32 (t, 2 H, J = 8 Hz)									7.5–7.3 (m, 5 H)
4c[c]	^{13}C	162.9	112.8	139.9	103.9	157.4	28.2	27.1	25.5	29.5	44.0				165.4			164.5	131–127
	^{1}H		6.91 (s, 1 H)				3.52 (t, 2 H, J = 4.5 Hz)	1.84–1.74 (m, 6 H)			4.40 (t, 2 H, J = 4.5 Hz)								7.5–7.3 (m, 5 H)
4d[c]	^{13}C	163.7	113.3	141.1	104.5	158.2	29.5	26.9	21.0	25.2	31.7	43.9			167.7			166.8	133–127
	^{1}H		6.85 (s, 1 H)				3.38 (t, 2 H, J = 10 Hz)	1.85–1.45 (m, 8 H)				4.25 (t, 2 H, J = 10 Hz)							7.5–7.29 (m, 5 H)

[a] In Me_2SO-d_6. [b] In CF_3COOH. [c] In $CDCl_3$.

Acknowledgment. Grateful acknowledgment is made to 3M for continued funding of this research and to Dr. Steve Heilmann of 3M Corporate Research for helpful discussions.

Registry No. **1a**, 43170-60-1; **1b**, 98303-90-3; **1c**, 98303-85-6; **1d**, 98303-92-5; **2**, 106420-73-9; **3b**, 106420-69-3; **3c**, 98303-86-7; **4b**, 106420-71-7; **4c**, 106420-70-6; **4d**, 106420-72-8; **5**, 68475-24-1; DMAD, 762-42-5; NPM, 941-69-5; (*E*)-$H_3CO_2CCH{=}CHCO_2CH_3$, 624-49-7; (*Z*)-$H_3CO_2CCH{=}CHCO_2CH_3$, 624-48-6; $H_2C{=}CHCO_2CH_2CH_3$, 140-88-5; 4-$O_2NC_6H_4COCH_3$, 100-19-6; 4-$H_3CC_3H_4NCO$, 622-58-2; $ClCH_2CONHCOC_6H_5$, 7218-27-1; dicyanocyclobutene, 3716-97-0.

Supplementary Material Available: Figure containing heteronuclear COSY spectrum for compound **3c** (1 page). Ordering information is given on any current masthead page.

Michael Additions of Nitroalkanes to α,β-Unsaturated Carbonyl Compounds Using KF/Basic Alumina

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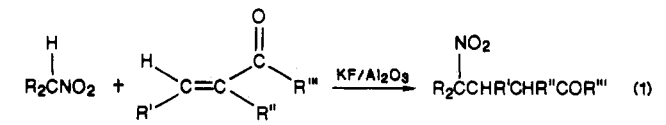
Catalysts and reagents supported on inorganic substrates have received increasing attention in recent years as a means to develop more convenient or selective catalysts or reagents.[1-3] In this context, potassium fluoride adsorbed on various sorts of alumina has commonly been used as a base. Such heterogeneous bases have been shown to be effective in both aldol condensations and Michael addition reactions. Adsorbing KF on neutral alumina greatly enhances the activity of this basic catalyst.[4,5] Other workers have also noted that the use of basic alumina as a support for KF leads to moderate yields of Michael addition products when reactions are carried out in the absence of solvent.[6] However, poor yields and low selectivity were obtained in the latter case for reaction of nitromethane and 3-buten-2-one. In the course of studying the chemistry of nitroparaffins and their derivatives, we have developed procedures using KF/basic alumina which are very effective at promoting Michael-type reactions between nitroparaffins and reactive Michael acceptors such as acrylate esters and α,β-unsaturated carbonyl compounds (eq 1). Unlike the procedures used by Rosini,[6] these



(1)

reactions proceed in the presence of a solvent (THF) and can be carried out on large scale. Our results resemble those obtained by Clark[5] using neutral alumina. However, while KF/neutral alumina forms mono-Michael adducts with *sec*-nitroalkanes as nucleophiles, the reaction of

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Table I. Michael Addition of Nitroalkanes to α,β-Unsaturated Carbonyl Compounds Using KF/Basic Alumina[a]

nitroalkane	Michael substrate	scale (mmol substrate)	KF/basic alumina (g)	yield,[b] %
CH_3NO_2	ethyl acrylate	9.2	5	77[c]
CH_3NO_2	ethyl acrylate	92	40[d]	39[e]
CH_3NO_2	1,3-diphenyl-2-propen-1-one	5	4	96
$CH_3CH_2NO_2$	ethyl acrylate	9.2	5	97[f]
$CH_3CH_2NO_2$	butyl acrylate	70	20	90
$CH_3CH_2NO_2$	4-methyl-3-penten-2-one	9	5	0
$CH_3CH_2NO_2$	3-buten-2-one	12	5	100
$CH_3CH_2NO_2$	2-cyclohexen-1-one	5	3	100
$CH_3CH_2CH_2NO_2$	ethyl acrylate	138	20	97
$CH_3CH_2CH_2NO_2$	1,3-diphenyl-2-propen-1-one	25	28	96
$CH_3CHNO_2CH_3$	butyl acrylate	7	5	99
$CH_3CHNO_2CH_3$	2-cyclohexen-1-one	5.2	3	100
c-$C_6H_{11}NO_2$	butyl acrylate	3.6	2	90[g]
c-$C_6H_{11}NO_2$	2-cyclohexen-1-one	5.2	3	77[g]

[a] Typically a 4–8-fold excess of the nitroalkane was shaken with in a THF suspension with the indicated amounts of substrate and KF/basic alumina for 2 h at 25 °C by which time GC analysis showed that the starting α,β-unsaturated carbonyl compound had been consumed. [b] Isolated yields of products characterized by ^1H NMR, ^{13}C NMR, and GC/MS. [c] 1% of the diadduct was present. [d] KF/neutral alumina was used in place of KF/basic alumina. [e] The product was a 3:1 mixture of mono- to diadduct. [f] The same scale reaction using only basic alumina (15 g) without any KF being present yielded 65% of the monoadduct after 2 days. [g] The nitroalkane was the limiting reagent in these reactions.

prim-nitroalkanes and nitromethane with acrylate esters using KF/neutral alumina was complicated by the formation of byproducts resulting from multiple Michael additions. We found that using our procedures described below that this byproduct formation was avoided by using basic alumina as the support. In addition, we found that these procedures were generally useful, leading in most cases to quantitative yields of adducts which did not require purification other than removal of the excess starting nitroalkane.

These KF/basic alumina promoted Michael reactions worked best with α,β-unsaturated carbonyl substrates that were not hindered at the β-carbon atom. Thus, while quantitative yields were obtained with methyl vinyl ketone, mesityl oxide did not react quantitatively. In some cases, use of additional base was successful in inducing further conversion of sluggish substrates (cf. 1,3-diphenyl-2-propen-1-one) to product. However, in reaction of 1,3-diphenyl-2-propen-1-one with nitromethane or 1-nitropropane, we found that only activation of the KF/basic alumina at 150 °C for 8 h and 1 torr was sufficient to achieve complete conversion of the enone to product.

Attempts to recycle the solid base used in these reactions had mixed results. In reactions where a large excess of KF/Al_2O_3 was used, we were able to successfully reuse the solid base after simply reheating it to 150 °C at 1 torr for 8 h. However when smaller amounts of solid base were used (e.g., 4 g of KF/Al_2O_3 with 9.2 mmol of ethyl acrylate and 33 mmol of 2-nitropropane), attempts to recycle the base led to incomplete (62%) conversion of the Michael substrate to the addition product. In such cases, the solid base could be recycled if it were re-treated with aqueous KF, dried, and activated at 150 °C for 8 h at 1 torr.

Table I lists some representative reactions showing the results of our studies. As can be seen, nitromethane, *prim*-nitroalkanes, and *sec*-nitroalkanes all yield high yields of pure Michael addition products with both enones and α,β-unsaturated carboxylic acid esters. While attempts to use KF/basic alumina as a reagent under our conditions yield Michael addition products containing both mono- and diaddition products, KF/basic alumina reactions produced only the monoaddition products. Control experiments showed that both KF alone and basic alumina alone were unable to carry out these reactions.

In summary, KF/basic alumina which has been activated under comparatively mild conditions is an effective base for Michael reactions of nitroalkanes with a variety of α,β-unsaturated carbonyl compounds. If excess nitroalkane is used, the products are formed in near quantitative yield. In such cases, pure products are easily isolated by removal of solvent. No additional distillation or purification steps are necessary.

Experimental Section

General Methods. Tetrahydrofuran (THF) was purified and dried by distillation from sodium benzophenone ketyl under an atmosphere of nitrogen. Other solvents were reagent grade and were used as such. Nitroalkanes and starting α,β-unsaturated carbonyl compounds were purchased from Aldrich Chemical Co. Volatile products from reactions were analyzed on a Varian Model 3700 or Hewlett-Packard 5830A gas chromatograph using a fused silica OV-17 capillary column and the products were further characterized by GC/MS using a Hewlett-Packard 5970A GC/MS system. ^1H NMR spectra were recorded on a Varian EM-390 spectrometer or on a Varian XL-200E spectrometer. ^{13}C NMR spectra were recorded on a Varian XL-200E spectrometer. The chemical shifts reported for ^1H and ^{13}C NMR spectra are relative to Me_4Si.

Preparation and Activation of KF/Basic Alumina. In a typical procedure, the KF/alumina base was prepared by dissolving 50 g of $KF{\cdot}2H_2O$ in 200 mL of water and adding 150 g of basic alumina. Chromatography grade basic alumina from both EM Reagents (70–280 mesh) and from Fisher (80–200 mesh) were both used with equal success. The resulting suspension was immediately placed on a rotary evaporator and the water was removed under reduced pressure. The resulting free flowing powder was dried at 1 torr at 150 °C for 8 h. Milder activation conditions (50 °C for 3 h at 1 torr) sufficed to prepare KF/basic alumina which was active enough to serve as a base for the more reactive substrates in Table I.

General Procedure for Michael Reactions. A typical procedure for Michael reactions is illustrated by the following preparative-scale reaction of ethyl acrylate and 1-nitropropane. In this reaction, 15 mL of ethyl acrylate (138 mmol) and 50 mL of 1-nitropropane (560 mmol) were dissolved in 750 mL of dry THF. Then 20 g of KF/basic alumina containing 3.5 mequiv of KF/g of alumina was added and the resulting suspension was shaken on a mechanical shaker for 2 h. At this point, GC analysis showed that the ethyl acrylate had been completely consumed. Workup was effected by simply filtering off the alumina, washing the alumina with two 50-mL portions of ethyl acetate, and then removing the THF, ethyl acetate, and excess 1-nitropropane using a rotary evaporator under reduced pressure. The product was obtained as a colorless oil and weighed 25.2 g (97% yield): ^1H NMR ($CDCl_3$) δ 4.45 (m, J = 4.6 Hz, 1 H), 4.10 (q, J = 7.0 Hz, 2 H), 1.65–2.40 (m, 6 H), 1.22 (t, J = 7.7 Hz, 3 H), 0.8 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.8, 89.1, 60.8, 30.2, 28.3, 27.2, 14.1, 10.2.

Procedure for Recycling the KF/Basic Alumina. The used KF/basic alumina was recycled by first washing with distilled water and then adding 4 g of the washed alumina to a solution of 1.7 g of $KF \cdot 2H_2O$ in 20 mL of distilled water. Removal of water and activation of the KF/basic alumina as described above yielded a fresh sample of the solid base. This recycled base was then used to effect a Michael reaction between 3 mL (33 mmol) of 1-nitropropane and 1 mL (9.2 mmol) of ethyl acrylate in 2 h at 25 °C, yielding 1.6 g (93%) of ethyl 4-nitrohexanoate after removal of solvent and excess 1-nitropropane as described above.

Acknowledgment. The support by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Robert A. Welch Foundation is gratefully acknowledged.

Registry No. CH_3NO_2, 75-52-5; $CH_3CH_2NO_2$, 29-24-3; $CH_3(CH_2)_2NO_2$, 108-03-2; $(CH_3)_2CHNO_2$, 79-46-9; CH_2=CHC(O)OEt, 140-88-5; PhCH=CHC(O)Ph, 94-41-7; CH_2=CHC(O)OBu, 141-32-2; $(CH_3)_2C$=CHC(O)CH_3, 141-79-7; CH_2=CHC(O)CH_3, 78-94-4; $NO_2(CH_2)_3C(O)OEt$, 2832-16-8; $NO_2(CH_2)_2CH(CH_2NO_2)C(O)OEt$, 106251-91-6; $NO_2CH_2CH(Ph)CH_2C(O)Ph$, 6277-67-4; $CH_3CH(NO_2)(CH_2)_2C(O)OEt$, 4093-53-2; $CH_3CH(NO_2)(CH_2)_2C(O)OBu$, 106251-92-7; $CH_3CH(NO_2)(CH_2)_2C(O)CH_3$, 35223-72-4; $CH_3CH_2CH(NO_2)(CH_2)_2C(O)OEt$, 59925-14-3; $CH_3CH_2CH(NO_2)CH(Ph)CH_2C(O)Ph$, 80460-05-5; $(CH_3)_2C(NO_2)(CH_2)_2C(O)OBu$, 91017-54-8; KF, 7789-23-3; nitrocyclohexane, 1122-60-7; 2-cyclohexen-1-one, 930-68-7; 3-(1-nitroethyl)cyclohexanone, 59969-93-6; 3-(2-nitroprop-2-yl)cyclohexanone, 4908-50-3; butyl 1-nitro-1-cyclohexanepropanoate, 106251-93-8; 3-(1-nitro-1-cyclohexyl)cyclohexanone, 106251-94-9; alumina, 1344-28-1.

Aldol-Equivalent Elaboration of Sterically Hindered Ketones: Methallylmagnesium Chloride as a Synthon for Acetone Enolate

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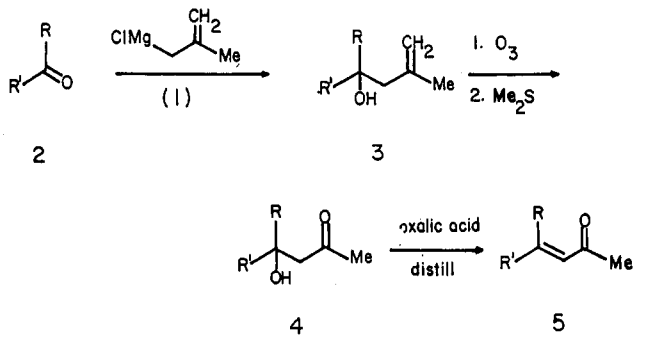
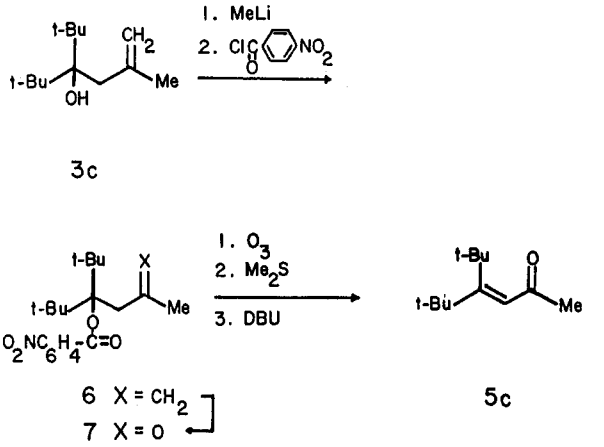
The aldol condensation has long been one of the most useful methods for the construction of carbon–carbon bonds. Modern variants on this venerable process, which allow the controlled cross-condensation of two dissimilar carbonyl compounds, have greatly extended the synthetic utility of the aldol reaction.[1] Nonetheless, important limitations still exist. For example, enolate additions to sterically hindered ketones are troublesome, presumably due to unfavorable equilibria for this reversible reaction. Likewise, additions to easily enolizable ketones often fail because of a kinetically preferred proton transfer.

Current interest in the preparation of organic compounds containing bulky substituents[2] led us to explore aldol-equivalent reactions which would be applicable to such hindered ketones. Bulky dialkyl ketones are readily available and would serve as useful starting materials for the preparation of such sterically encumbered molecules. We report here a successful procedure for the three-carbon,

Scheme I



Scheme II



aldol-equivalent homologation of ketones (Scheme I), which should be of particular value in the elaboration of sterically hindered and easily enolized ketones.

Our approach to this problem is based on the synthetic equivalence of methallylmagnesium chloride (1) with the enolate of acetone.[3,4] Upon addition of the organometallic reagent to a ketone, the latent carbonyl group of 1 can be unmasked by ozonolytic cleavage of the terminal alkene. Several ketones were investigated. The results are summarized in Table I. In all cases, addition of methallylmagnesium chloride was accomplished in a straightforward manner and in high yield. The well-documented reversibility of allyl organometallics to hindered ketones[5] poses no problem—the equilibrium strongly favors the addition product. Even readily enolizable ketones such as cyclopentanone and camphor undergo efficient addition of the methallyl Grignard reagent, in accord with the observation that allylic organometallics rarely cause enolization of carbonyl substrates.[6] Only a single stereoisomeric product was detected in the addition to camphor. This is formulated as the exo alcohol **3e**, by analogy to the literature precedent.[7]

Ozonolysis of the homoallylic alcohols **3a–e** proceeds quite cleanly and in excellent yield to give the corre-

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