In addition to hydrogenolysis, hydrogen addition was also observed (as the major reaction) in the case of nitro and (surprisingly) cyano groups. The major products from *p*-bromonitrobenzene and *p*-bromobenzonitrile were *p*-bromoaniline and *p*-bromobenzylamine, respectively. While the cyano group is apparently easy to reduce under these conditions, it is interesting to note that the carbomethoxy group is unaffected (Table II).

Since the variety of yields in Table II indicated an obvious substituent effect, individual rates were measured and compared in a Hammett plot, excluding those which exhibited addition reactions. The slope was found to have a ρ value of +3.38 for the positive σ substitutents ($r = 0.950$), implying a nucleophilic transition state. For *p*-bromo-*N*,*N*-dimethylaniline and the other negative σ substituents, the ρ value is much closer to 0 ($\rho = 0.10$, $r = 0.90$), indicating a different kind of transition state of a much less polar nature (possibly a change of mechanism to form the arylphosphonium salts). Also, the dimeric products noted in Tables I and II suggest aryl radical intermediates. Very similar results have been observed for the nickel(0)-catalyzed cyanation in ethanol.[5]

This reaction may be synthetically useful under relatively simple conditions, provided DMF is used as solvent and in the absence of other easily reduced functional groups, phenols, and unsubstituted anilines.

Experimental Section

Apparatus. Gas chromatography was performed with Varian Aerograph 90-P or 1700 gas chromatographs fitted with thermal conductivity detectors. High-performance liquid chromatography was performed with a Waters instrument fitted with a C_{18} reverse-phase column, using acetonitrile–water (70:30) as mobile phase. NMR spectra were recorded with a Varian A-60D spectrometer.

Materials. *p*-Bromotoluene, *p*-bromochlorobenzene, *p*-bromonitrobenzene, and *p*-bromobenzonitrile were prepared by standard methods modified from ref 7 and purified by recrystallization or vacuum distillation before use. Methyl *p*-bromobenzoate and *p*-bromoanisole were prepared after the procedure of ref 8, *p*-bromophenol after ref 9, and *p*-bromo-*N*,*N*-dimethylaniline after ref 10. *p*-Dibromobenzene and dimethyl sulfoxide were purchased from J. T. Baker and used without further purification. *p*-Bromoaniline was from Eastman Kodak. THF, HMPT, $NaBH_4$, and triphenylphosphine were from Aldrich. The DMF was from Matheson Coleman and Bell and was redistilled before use.

Catalyst Preparations. Bis(triphenylphosphine)nickel(II) was prepared after the method of Venanzi.[11]

The nickel(II) complex was converted to the nickel(0) catalyst by two different methods. (1) After heating 10 mL of DMF to 70 °C under nitrogen gas for 30 min, the nickel(II) complex from above (0.13 g, 0.2 mmol), triphenylphosphine (0.11 g, 0.4 mmol), and zinc dust (0.07 g, 1 mmol) were added. The characteristic deep red color of the tetrakis(triphenylphosphine)nickel(0) was formed within 45–50 min.[12] (2) The same procedure as 1 was used, except that $NaBH_4$ (0.01 g, 0.27 mmol) was substituted for the zinc dust. This method was used for all runs, except those indicated.

General Procedure for Dehalogenation. After preparing the catalyst solution as above, the temperature (70 °C) and nitrogen atmosphere were maintained and the mixture was stirred for 30 min. The aromatic halide (4.0 mmol) was then added, and conditions were maintained for another 30 min. Sodium borohydride (0.37 g, 4.0 mmol) was then added and the mixture stirred at 70 °C for 3–20 h with periodic GLC analysis.

For kinetic runs, a similar procedure was followed. A narrow-neck tube fitted with a rubber septum was first charged with 1 mmol of aromatic halide and then evacuated.[13] Then freshly prepared solutions of Ni(II) complex in DMF (2.5 mL, 0.04 M) and $NaBH_4$ in DMF (2.5 mL, 0.48 M) were also introduced via syringe. The solutions were prepared and mixed in a drybox filled with nitrogen. Once mixed, the tube was filled to 1 atm with nitrogen, removed from the drybox, and emersed in a 50 °C oil bath. Samples were periodically removed via syringe (4 μL) for GLC analysis by direct injection of the reaction mixture; preliminary experiments had demonstrated that no dehalogenation reaction occurrred in the hot GLC injector.

Rate measurements were duplicated at least once each, and reproducibility was ±2% or better. Rates were measured as the decrease in Ar–X concentration via GLC peak area determination. Under catalytic conditions (0.1 M dibromobenzene and 0.005 M Ni(II)), the reaction was found to be first order in Ni complex; by halving the Ni concentration the rate dropped from 5.14×10^{-1} to 2.60×10^{-1} h^{-1}.

Registry No.—$NaBH_4$, 16940-66-2; $Ni(Ph_3P)_2Cl_2$, 14264-16-5; $Ni(Ph_3P)_3$, 25136-46-3.

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General, Efficient, One-Step Synthesis of β-Keto Esters

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β-Keto esters form a large part of the important class of 1,3-dicarbonyl compounds and, as such, have enjoyed a long history of diverse chemical preparations and use in synthesis. Their popularity is based on several factors, one of which is facile bond formation with the two, differentiable, electrophilic carbonyls and either of the nucleophilic α or γ sp^3 carbons.

As part of a program in our laboratory on pyrimidine chemistry, we needed to exploit these attributes of β-keto esters and, therefore, required an economical and efficient preparation. Although nearly all possible routes of synthesis of β-keto esters have been conceptualized and reduced to practice in specific and general approaches,[1-3] we felt a reasonable incentive for improvement existed in the more pragmatic aspects such as economical availability of starting materials, yields, purifications necessary, competing side reactions, and scale-up requirements.

In 1959 Ireland and Marshall[1b] reported that the magnesium salt of α-substituted malonyl monoesters yielded β-keto esters in 50–70% yields upon reaction with acid chlorides.[1f] We have found that dilithio dianion of monoethyl malonate reacts with acid chlorides to afford β-keto esters directly in excellent yield and without need of further purification.

Treatment of monoethyl malonate[4] in tetrahydrofuran (THF) with 2 equiv of *N*-butyllithium from −30 °C with slow warming to −5 °C yields a heterogeneous solution. The reac-

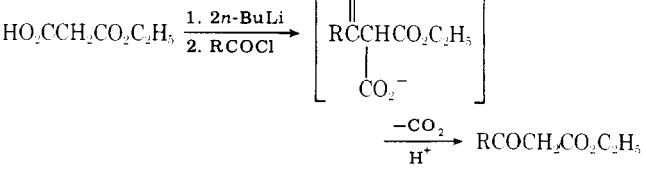

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Table I

$$RCOCl + [CH(CO_2C_2H_5)CO_2]^{2-}\ 2Li^+ \xrightarrow{THF} RCOCH_2CO_2C_2H_5$$

R	registry no.	reaction time, min	isolated yield,[a,b] %	registry no.	NMR ($CDCl_3$)[c]
$CH_3CH_2CH_2$	141-75-3	5	95	3249-68-1	3.41 (s, 2 H), 2.75–2.38 (q, 2 H), 1.50–0.86 (m, 6 H)
$(CH_3)_2CHCH_2$	108-12-3	5	98	34036-16-3	3.50 (s, 2 H), 2.96–2.41 (m, 1 H), 1.46–1.0 (m, 9 H)
$CH_3(CH_2)_2CH_2$	638-29-9	5	97	7737-62-4	3.43 (s, 2 H), 2.65–2.41 (m, 2 H), 1.91–0.8 (m, 8 H)
$PhCH_2$	103-80-0	5	99	718-08-1	3.38 (s, 2 H), 7.25 (m, 5 H), 3.78 (s, 2H)
Ph	98-88-4	30	97	94-02-0	8.06–7.25 (m, 5 H), 5.66 (s, 0.2 H), 3.97 (s, 1.8 H)
4-CH_3Ph	874-60-2	30	91	27835-00-3	8.05–7.01 (m, 4 H), 5.63 (3, 0.15 H), 2.40 (s, 3 H)
4-CH_3OPh	100-07-2	60	90	2881-83-6	7.94 (d, 2 H), 6.95 (d, 2 H), 3.92 (s, 2 H), 3.86 (s, 3 H)
3,4-Cl_2Ph	3024-72-4	30	97	53090-43-0	8.06–7.50 (m, 3 H), 5.63 (s, 0.3 H), 3.93 (s, 1.43 H)
4-CNPh	6068-72-0	30	88	49744-93-6	7.78 (A_2B_2, 4 H), 5.72 (s, 1.1 H), 4.02 (s, 0.9 H)
3-IPh	1711-10-0	30	97	68332-33-2	8.4–7.5 (m, 3 H), 7.4–7.0 (m, 1 H), 5.65 (s, 0.3 H), 3.96 (s, 1.7 H)
4-$(CH_3)_2NPh$	4755-50-4	60, 60 to 0 °C	76	54441-61-1	7.85 (d, 2 H), 6.63 (d, 2 H), 3.89 (s, 2 H), 3.01 (s, 6 H)
2-$C_{10}H_7$	40079-92-3	30	95	68332-34-3	8.40 (m, 1 H), 8.1–7.4 (m, 6 H), 5.78 (s, 0.15 H), 4.07 (s, 1.8 H)
3-furyl	26214-65-3	120	97	36878-91-8	8.13 (m, 1 H), 7.49 (m, 1 H), 6.83 (m, 1 H), 5.40 (s, 0.1 H), 3.77 (s, 1.9 H)
2-ClPh	609-65-4	60	93	19112-35-7	7.7–7.2 (m, 4 H), 5.53 (s, 0.25 H), 4.01 (s, 1.75 H)

[a] Based on acid chloride. [b] All purities more than 90% as determined by either GLC or ^1H NMR. The only contaminant appears to be hydrocarbons including *n*-octane. [c] Resonances excluding ethyl ester.

tion is recooled to ca. −65 °C, the acid chloride is added, and the cooling is removed. The work-up procedure simply involves quenching the reaction at the appropriate time with dilute acid followed by extraction with ether. The organic phase is washed with bicarbonate, dried, and concentrated to yield the desired β-keto ester. The generality of this one-pot process is supported by the examples summarized in Table I.

It is important to note that excess malonyl dianion is required for high conversion to β-keto esters. The optimum ratio of malonate to acid chloride is 1.7 (or greater) for highest yields. For example, the yield of ethyl propionylacetate drops to 82% at a ratio of 1.5 and 76% at 1.0.[5] Since the monoethyl malonate is inexpensive, readily available, and easily removed from the reaction during workup, its use in excess detracts little from the utility of this process. The use of HMPA in addition to THF, or LDA instead of *n*-BuLi, results in much poorer yields. The scale-up of this process to 2-mol reproducibly exhibited the same high yields reported in Table I.

We believe this process has the superior attributes of high yields, absence of a purification requirement, ease of operation, and attractive economics.

Experimental Section

General. Reagent tetrahydrofuran was distilled from sodium/benzophenone under N_2 prior to use. Acid chlorides which were not commercially available were prepared from the corresponding acids by the standard procedures using thionyl chloride, except for *p*-dimethylaminobenzoyl chloride.[6]

^1H NMR were recorded on either a Varian A-60A or HFT-80 in $CDCl_3$ with internal Me_4Si. GC–MS data[7] were recorded on a Hewlett-Packard 5992A with GLC data determined on a Hewlett-Packard 402 with a 4 ft 3% OV-17 glass column and He carrier gas.

General Procedure. To 250 mL of THF under N_2 with stirring is added 13.47 g (0.1 mol) of monoethyl malonate and several milligrams of 2,2′-bipyridyl as an indicator. After cooling to −70 °C, *n*-butyllithium (hexane) is added slowly while allowing the temperature to rise to ca. −5 °C near the end of the addition (~130 mL of 1.6 M solution, 0.2 mol). After the pink indicator persists at −5 °C the heterogeneous solution is recooled to −65 °C and the acid chloride (0.057 mol) is added dropwise over 5 min. After the appropriate reaction time (Table I), the reaction solution is poured into 400 mL of ether and 200 mL of 1 N hydrochloric acid. After mixing and separating the aqueous phase, the organic phase is washed with 2 × 100 mL of saturated bicarbonate and 100 mL of water, dried over anhydrous sodium sulfate, and concentrated in vacuo to yield the β-keto ester.

In those cases where the product contains a basic nitrogen the workup includes adjusting the initial aqueous ether extraction to ca. pH 7.

Registry No.—Monoethyl malonate dilithium salt, 68332-35-4.

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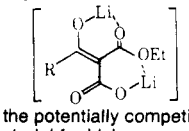
(4) Readily prepared from diethyl malonate by the procedure of R. E. Strube, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 417, or from the commercially available potassium monoethyl malonate.

(5) The high-yield requirement of excess monoethyl malonate dianion is not readily apparent since the product, prior to workup, already exists as the lithium salt after in situ decarboxylation. Perhaps deprotonation of the presumed initial intermediate, $[RCOCH(CO_2Et)CO_2Li]$, to



as a means of "storing" the potentially competitive reactant, requires the use of excess starting material for high conversion to β-keto ester.

(6) French Patent, 1 482 866 (1967) (*Chem. Abstr.*, **69**, 19143v (1968)).

(7) All of the β-keto esters are known compounds. Identification by GC–MS or elemental analysis (±0.4%) confirmed the structural assignments in addition to the NMR data given in Table I.

(8) The use of Meldrum's acid in a versatile, two-step preparation of β-keto esters was just reported: Y. Oikawa, K. Sugano, and O. Yonemitsu, *J. Org. Chem.*, **43**, 2087 (1978).