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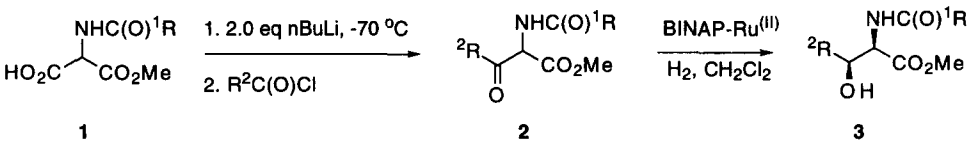
A Practical Synthesis of α-Acylamino-β-Keto-Esters: Acylation of Alkyl Hydrogen (Acylamino)malonates via the $MgCl_2/R_3N$ Base System

Damian J. Krysan

Hoechst Marion Roussel Inc.,
2110 East Galbraith Road, Cincinnati, OH 45215

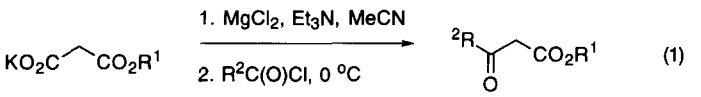
Abstract: An operationally simple procedure for the synthesis of α-acylamino-β-keto-esters has been devised using a $MgCl_2/R_3N$ base system to generate the magnesium enolates of a series of alkyl hydrogen (acylamino)malonates. These reagents smoothly react at 0 °C with a variety of acid chlorides to give α-acylamino-β-keto-esters in good to excellent yields. In addition to being quite convenient and versatile for small scale preparations, the method should also be well suited to the large scale synthesis of this important class of molecules.

Scheme 1



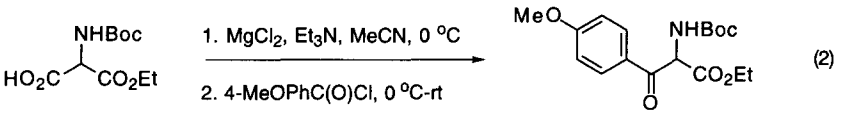
1 2 3

As part of a recent total synthesis effort in these laboratories, we had occasion to study the preparation of a series of α-acylamino-β-keto-ester derivatives (**2**). This class of compounds represents an important set of substrates for the synthesis of enantiomerically enriched, *erythro*-α-acylamino-β-hydroxy-esters (**3**) by dynamic resolution using Noyori's Ru-BINAP catalyzed hydrogenation methodology.[1] Within this context, Schmidt and co-workers have recently reported an attractive approach to the synthesis of the title compounds wherein the dilithium salts of a series of alkyl hydrogen (acylamino)malonates (**1**) are acylated with a variety of acid chlorides (Scheme 1).[2] Although Schmidt's method used cheap, readily available starting materials, we were concerned that its reliance on multiple equivalents of alkyllithium base at ultra-low temperature would make it impractical for large scale synthesis. In this report, we describe a simpler and more practical set of reaction conditions for this chemistry based on the use of a $MgCl_2/R_3N$ base system.



4 5 (1)

The synthesis of β-keto esters by the acylation of malonate derived enolates has been extensively studied over the years and a number of reaction conditions, bases, and acylating agents have been developed depending on the demands of the specific application.[3] Of these various modifications, we were particularly interested in a recent report by Wemple and co-workers[4] which described the use of Rathke's $MgCl_2/R_3N$ protocol[5] in the large scale synthesis of β-keto esters (eq 1). We felt that successful application of Wemple's procedure to the alkyl hydrogen (acylamino)malonate substrates would not only solve our immediate scale up problems but also offer a convenient and general approach to the synthesis of α-acylamino-β-keto esters.



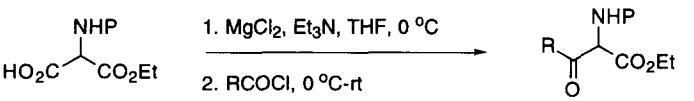
1a (82%) 2a (2)

In the event, treatment of an ice cold acetonitrile solution of malonate **1a**[2] (2.0 equiv) with E_3N (4.1 equiv) and $MgCl_2$ (2.1 equiv) gave a white slurry which was stirred for 2.5 hr. The resulting metallated malonate (*vide infra*) was then treated with an acetonitrile solution of 4-methoxybenzoyl chloride (1 equiv) and stirred overnight at room temperature. Standard work-up then provided α-acylamino-β-keto ester **2a** in 82% yield.

Encouraged by the initial success of this approach, a brief optimization study was undertaken wherein a selection of reaction parameters was varied. Three different solvents were examined, including acetonitrile, THF, and dichloromethane and all gave comparable results. Both triethylamine and diisopropylethylamine were shown to provide good yields, although triethylamine may be better suited for large scale work since it gives a more easily stirred suspension in THF and acetonitrile. The number of equivalents of malonate can be reduced to 1.5 in some systems, although each substrate should be optimized separately for best results. Furthermore, it is recommended that initial experiments be performed with 2 equivalents of malonate since consistently good yields have been observed with this stoichiometry regardless of substrate properties and since no improvements in yield have been observed with more than two equivalents of malonate. Finally, it has also been possible to execute small scale experiments (1-10 mmol) entirely at ambient temperature without difficulty. However, since the metallation step is moderately exothermic, large scale preparations are best done by performing both the metallation reaction and the acid chloride addition at 0 °C.[6]

As shown in the Table, the method has been tested with a number of different aroyl- and alkoyl chlorides. In general, the aroyl chlorides reacted to give slightly higher yields than the alkoyl chlorides. Electron rich and electron deficient aroyl chlorides reacted with equal efficiency. In the alkoyl chloride series, primary and secondary alkoyl halides gave good yields. The reaction was, however, found to be somewhat sensitive to steric hindrance in that pivaloyl chloride reacted to give only a trace (5-10% estimated yield) of the desired β-keto ester product.

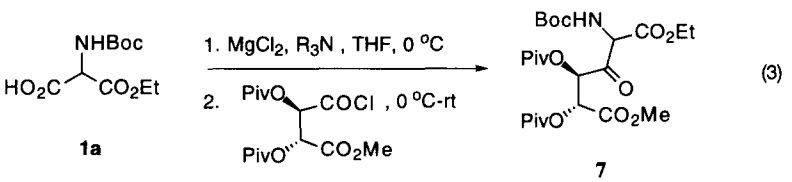
Table. Scope of α-Acylamino-β-Keto-Ester Synthesis.



1 **2**

Entry	Malonate	P	RCOCl	Product	Yield
1	**1a**	Boc	4-MeOPh-	**2a**	82%
2	**1a**	Boc	Ph-	**2b**	87%
3	**1a**	Boc	4-F-3-NO_2Ph-	**2c**	90%
4	**1a**	Boc	Me-	**2d**	65%
5	**1a**	Boc	*n*-Pn-	**2e**	75%
6	**1a**	Boc	*i*-Pr-	**2f**	71%
7	**1a**	Boc	Me_3C-	**2g**	trace
8	**1b**	Cbz	Ph-	**2h**	86%
9	**1c**	Bz	Ph-	**2i**	92%
10	**1d**	Ac	Ph-	**2j**	trace

In addition to the Boc-protected aminomalonate (**1a**), three other common nitrogen protecting groups have been investigated. The CBZ (**1b**) and benzamide (**1c**) protected substrates were found to give good yields of β-keto ester product, while the acetamide (**1d**) substrate failed to give more than a trace of the desired material. Although the chemistry of **1d** has not been thoroughly studied, it is possible that the potentially enolizable protons of the acetamide moiety may interfere with the acylation reaction in this instance.



1a **6** **7** (3)

$R_3N = Et_3N$, 0 % yield of **7**

$R_3N = {}^iPr_2EtN$, 70-75% yield of **7**

Finally, we have also applied this chemistry to a more complex and functionally delicate substrate as shown in equation 3. The tartrate derived acid chloride **6**, prepared according to Duhamel and co-workers,[7] was reacted with Boc-protected aminomalonate **1a** using the general procedure. Not surprisingly, none of the desired β-keto ester was detected under these conditions and a control experiment showed that **6** was not stable

in the presence of triethylamine. Considering that substrate **6** could be susceptible to base mediated β-elimination as well as to ketene formation, it was thought that using the more sterically hindered diisopropylethylamine in place of triethylamine might lead to a successful coupling by suppressing interactions between the base and the acid chloride substrate. Indeed, in the presence of diisopropylethylamine a smooth reaction ensued to give the desired β-keto ester (**7**) in 70-75% yield with no detectable epimerization.

In conclusion, we have developed an important modification of Schmidt's α-acylamino-β-keto ester synthesis in which a base derived from the combination of $MgCl_2$ and a trialkylamine is used to metallate a series of alkyl hydrogen (acylamino)malonates at the easily obtained temperature of 0 °C. The resulting magnesium enolates react with a wide range of acid chlorides to give the corresponding α-acylamino-β-keto esters in good to excellent yields. The simplicity and convenience of this chemistry is noteworthy and should allow for its application to the large scale synthesis of this important class of molecules.

References and Notes

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6. **Representative Procedure**: An ice cold THF (10 mL) solution of **1a** (0.51 g, 2.1 mmol, 2.1 equiv) was treated with Et_3N (0.43 g, 4.3 mmol, 4.3 equiv) followed by $MgCl_2$ (0.23 g, 2.3 mmol, 2.3 equiv). The resulting slurry was stirred at 0 °C for 2.5 hr. A THF (5 mL) solution of 4-MeOPhCOCl (0.17 g, 1.0 mmol, 1.0 equiv) was added and, after 5 min, the cooling bath was removed. The mixture was allowed to stir for 12 hr at ambient temperature, after which time TLC (or GC) showed no remaining acid chloride. The reaction was quenched with aqueous citric acid and extracted with EtOAc. The organic extract was washed with additional citric acid, sat $NaHCO_3$, and brine before being dried (Na_2SO_4) and concentrated. The crude product (>90 pure by GC) was purified by flash silica gel chromatography (30% EtOAc/70% heptane, R_f 0.3) to give **2a** (0.28 g, 82%) as a pale yellow oil. 300 MHz ^1H NMR ($CDCl_3$) δ 8.11 (2H, d, *J* = 9.0 Hz, *o*-Ar*H*), 6.97 (2H, d, *J* = 9.0 Hz, *m*-Ar*H*), 5.89 (2H, overlapping doublets, N*H* & C*H*N), 4.16 (2H, m, OCH_2), 3.89 (3H, s, OCH_3), 1.46 (9H, s, $C(CH_3)_3$), 1.17 (3H, t, *J* = 7.1 Hz, CH_2CH_3). 75 MHz ^{13}C NMR ($CDCl_3$) δ 164.52, 155.06, 132.23, 132.05, 113.93, 80.47, 62.23, 59.16, 55.58, 28.56, 14.19, 13.91. IR (neat) 3369, 3065, 1747, 1724, 1698 cm^{-1}. MS (CI/NH_3) *m/e* 355 ($M+NH_4^+$), 338 ($M+H^+$), 238, 135. Anal. Calcd. for $C_{17}H_{23}O_6N$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.68; H, 6.85; N, 4.05.
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