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Solid-Phase *C*-Acylation of Active Methylene Compounds

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Abstract: Active methylene compounds were attached to the Wang resin by an ester linkage. *C*-acylation was achieved with a reactive species generated *in situ* by the combination of a carboxylic acid, diethyl phosphorocyanidate, and triethylamine. Cleavage from the resin with simultaneous decarboxylation gave the products in moderate to good yield.

Combinatorial methods for the generation of compound libraries have recently received tremendous attention, particularly for accelerating the drug discovery process.[1] This has resulted in a resurgence of interest[2] in extending solid-phase techniques beyond the traditional areas of peptide and nucleotide synthesis. Although the number of organic reactions adapted to solid-phase conditions is steadily increasing, many gaps in the synthetic repertoire still remain.

Active methylene compounds containing two electron-withdrawing groups are versatile precursors for the preparation of numerous pharmaceutically important heterocycles. A number of groups have focused on the solid-phase reactions of such compounds, *viz.* β-ketoesters,[3] β-ketoamides and β-amidonitriles,[4] and β-diketones.[5] Exploitation of the chemistry of the corresponding enolates has mainly centred on Knoevenagel condensation, α-alkylation, and γ-alkylation (via the dianion). The feasibility of *C*-acylation has not been explored,[6] although it would produce compounds with up to three different functional groups capable of further selective transformations.

Among existing solution-phase methods,[7] the combination of a carboxylic acid and diethyl phosphorocyanidate (DEPC) was first shown[8] to effect heteroatom (N, O, and S) acylation, and later demonstrated[9] to be efficient in *C*-acylation of 1,3-diactivated methylene compounds. From the standpoint of combinatorial chemistry, the mild reaction conditions (tertiary amine base, room temperature) were noteworthy. Another commendable feature was the direct use of readily available carboxylic acids activated[10] *in situ* rather than a preformed acyl chloride or other active ester intermediate.

Our first attempt was performed with cyanoacetic acid linked to the Wang resin (**Scheme 1**). The resin-bound β-cyanoester **1** was mixed with benzoic acid and DEPC in the presence of triethylamine to afford β-

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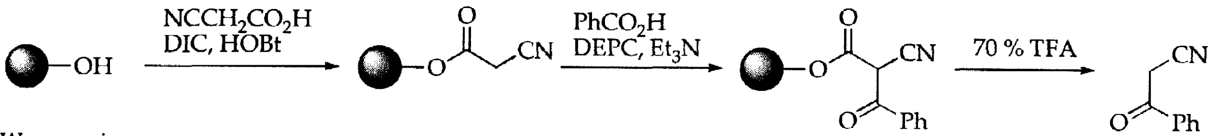
ketoester **2**. Resin cleavage with concomitant decarboxylation afforded benzoylacetonitrile **3** in 80 % isolated yield based on the initial capacity of the resin.[11]

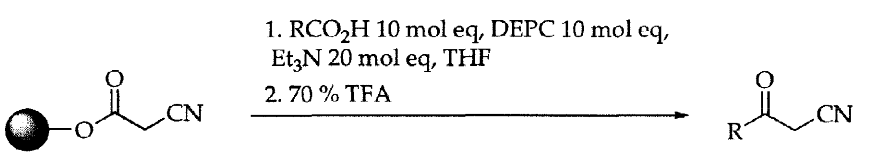
Scheme 1



Wang resin 1 2 3

Further studies (Table 1) established the scope of these acylations. The reagent quantities can be reduced from 10 molar equivalents to 5 without significant loss in yield (entry 2). Substitution of triethylamine by other bases (tetrabutylammonium fluoride, sodium hydride, sodium hexamethyldisilazane, entries 3-5) was much less successful. Among the aromatic carboxylic acids tried, anthranilic acid (entry 9) gave the poorest yield, possibly due to competing self-condensation. Premixing the acid with DEPC and triethylamine before portionwise addition to the resin (entry 10) resulted in an improved yield. Aliphatic carboxylic acids (entries 11-14) are generally poor substrates (similar trends were reported[12] in solution-phase *C*-acylation) although repeating the acylation (entry 12 vs. 13) helps.

Table 1. *C*-Acylation of Resin-bound Cyanoacetate.

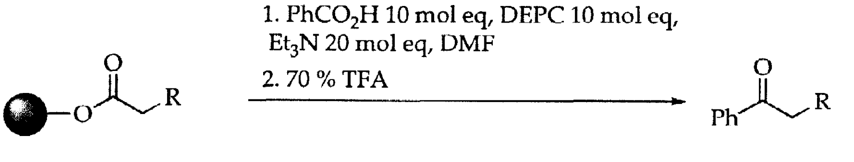


Entry	R	Yield (%)[a]	Entry	R	Yield (%)[a]
1	C_6H_5	80	8	4-I-C_6H_4	68
2	C_6H_5	74[b]	9	2-NH_2-C_6H_4	30
3	C_6H_5	48[c]	10	2-NH_2-C_6H_4	59[f]
4	C_6H_5	16[d]	11	$C_6H_5CH_2$	41
5	C_6H_5	0[e]	12	4-NO_2-$C_6H_5CH_2$	30
6	4-MeO-C_6H_4	78	13	4-NO_2-$C_6H_5CH_2$	48[g]
7	4-Et_2N-C_6H_4	48	14	$C_2H_5CH(CH_3)CH_2$	38

[a]Isolated yield after chromatography, based on the manufacturer's loading of the Wang resin. All compounds were characterized spectroscopically. [b]5 mol eq each of benzoic acid and DEPC, 10 mol eq of Et_3N, were used. [c]TBAF was used as base instead of Et_3N. [d]NaH was used as base instead of Et_3N. [e]NaHMDS was used as base instead of Et_3N. [f]Acid, DEPC, and Et_3N premixed and added portionwise. [g]Acylation was repeated.

We have also investigated the acylation of five other resin-bound active methylene compounds (Table 2), but isolated product yields were lower. This is consistent with the solution-phase results,[9] where the DEPC/triethylamine combination works best with cyano- and nitro-stabilized carbanions. Entry 4 shows that the thiophenyl group is insufficiently activating for these acylations, which can be remedied by oxidation to the sulfone (entry 5).

Table 2. *C*-Benzoylation of Other Active Methylene Compounds.



Entry	R[a]	Yield (%)[b]
1	2-NO_2-C_6H_4	42
2	$P(O)(OEt)_2$	23
3	CO_2Me	11
4	SC_6H_5	0
5	$SO_2C_6H_5$	45

[a]The esters in entries 1-4 were prepared in the same way as cyanoacetate **1**. The sulfone in entry 5 was generated from the resin-bound sulfide (entry 4) by *m*-CPBA oxidation. [b]Isolated yield after chromatography, based on the manufacturer's loading of the Wang resin. All compounds were characterized spectroscopically.

In this initial study, our primary goal was to determine the success of solid-phase acylations. Hence, products were immediately cleaved from the resin and yield quantified. Future applications will focus on the utilization of acylated resin-bound species for further reactions.

ACKNOWLEDGMENT

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