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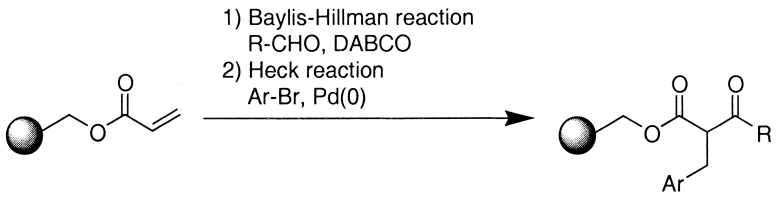

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Articles

Solid-Phase Synthesis of β-Keto Esters via Sequential Baylis−Hillman and Heck Reactions

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Acrylic acid was immobilized on polystyrene−Wang resin, followed by Baylis−Hillman reaction with aldehydes using DABCO as catalyst. Addition of 1 equiv of lanthanum(III) trifluoromethanesulfonate was found to improve yields, as in solution phase. After the Baylis−Hillman step, Heck reaction with aryl halides resulted in α-substituted β-keto esters, which were cleaved from the resin by acid hydrolysis with concomitant decarboxylation to afford aryl ketone products. Overall yields of 0−49% were obtained with 26 examples.

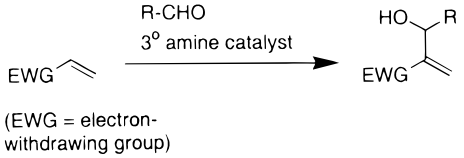
Introduction

Combinatorial chemistry[1] is firmly established as part of the drug discovery process and is also finding increasing application in areas such as materials science and catalysis. As a consequence, the development of reactions amenable to parallel synthesis has become the fastest growing area of organic chemistry within this decade. Much of this effort has been devoted to solid-phase techniques,[2] due to the ability to easily effect phase separation[3] between reagents and an immobilized substrate.

While the original solid-phase peptide and oligonucleotide syntheses exclusively involve heteroatom−heteroatom and carbon−heteroatom bond formation, current interest in small-molecule libraries has created a need for carbon−carbon bond formation as well. Nevertheless, compared to heteroatom bond formation, there is a dearth of such reactions that are sufficiently general and proceed with reliably high yields. For these reasons, we have been exploring various carbon−carbon bond forming reactions on solid phase and have previously reported cyclative Claisen-type condensations,[4] C-lithiation of heterocycles,[5] C-acylation,[6] and intermolecular radical reactions.[7]

The Baylis−Hillman reaction[8] (Scheme 1) has several attractive features for combinatorialization. The product contains three functional groups capable of further independent transformation. Unlike most carbon−carbon bond forming reactions, it can proceed at ambient temperature without requiring an inert atmosphere. Recent advances have also resulted in procedures for rate enhancement[9] as well as asymmetric induction.[10] Here, we report[11] our solid-phase studies with the reaction.

Scheme 1



Results and Discussion

We began with the attachment of acrylic acid to the polystyrene−Wang resin, followed by Baylis−Hillman reaction with various aldehydes. Initially, we examined Michael addition of amines as a route to functionalization of the adduct and identified the β-amino acid product (Scheme 2) after resin cleavage by trifluoroacetic acid (TFA). Meanwhile, similar Michael additions to Baylis−Hillman products on solid phase were reported.[11] We then investigated further reactions of the Michael adduct involving cyclization to β-lactams or azetidines. While the former[12] could be accomplished in model studies (Scheme 3), yields were variable. Attempted cyclization to an azetidine under Mitsunobu conditions[13] or prior conversion of the alcohol to a bromide was thwarted by elimination instead.

We next focused on Heck reactions[14] of the Baylis−Hillman adduct. The Heck reaction has proven to be a powerful means of solid-phase carbon−carbon bond formation. In this case, as shown in recent solution-phase studies,[15] the β-hydride elimination of the organopalladium intermediate is regioselective, exclusively giving rise to α-substituted β-keto esters which are important intermediates in heterocycle synthesis. Previously, solid-phase preparation[16] of such compounds has involved alkylation of β-keto esters, and we considered the tandem Baylis−Hillman−Heck sequence to be an alternative route of interest.

Our first solid-phase example (Scheme 4) was followed by TFA cleavage to release the free β-keto acid, which

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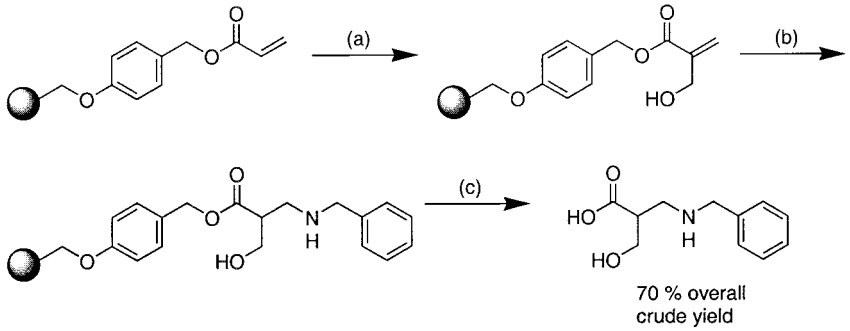
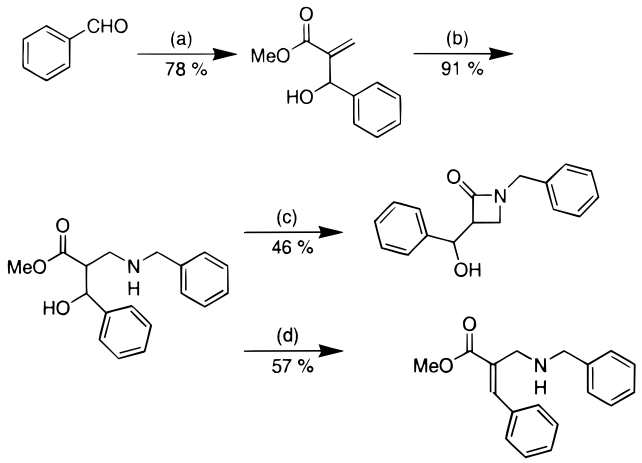
Scheme 2[a]



[a] Reagents and conditions: (a) HCHO (20 equiv), DABCO (20 equiv), $La(OTf)_3$ (1 equiv), 3:1 DMF/CH_3CN, 24 h; (b) $C_6H_5CH_2NH_2$ (20 equiv), CH_2Cl_2, reflux 4 h; (c) 50% TFA:CH_2Cl_2, 1 h.

Scheme 3[a]



[a] Reagents and conditions: (a) methyl acrylate (1.2 equiv), DABCO (1.1 equiv), $La(OTf)_3$ (0.05 equiv), CH_3CN, 24 h; (b) $C_6H_5CH_2NH_2$ (1.2 equiv), MeOH reflux, 3 h; (c) $(Me_3Si)_2LiN$ (4.2 equiv), THF −78 °C to rt, 4 h; sat. aq. NH_4Cl; (d) Ph_3P (1.1 eqiv), DEAD (1.1 equiv), CH_2Cl_2, 4 h.

decarboxylates in situ to give 1,3-diarylpropanone **1a**. Initially, in line with the solution-phase precedent,[15a] we used $Pd(OAc)_2$ as a catalyst for the Heck reaction. Later, we found this reagent to be unsuitable for substituted bromobenzenes, as previously noted[17] on solid phase, and switched to a Pd(0) catalyst. To determine if the final TFA acidolysis was quantitative, we also examined a second means of product release. Treatment with hydrazine resulted in cyclative formation of the pyrazolone **2**.[16,18] As yields were comparable, we used the TFA method in subsequent experiments.

Since little was known about solid-phase Baylis−Hillman reactions, we tried a number of conditions, followed by the standard Heck arylation and TFA cleavage, and quantified the yield of **1a** (Table 1). Extended reaction times beyond several days, or repeating the reaction, did not result in significant improvement. Microwave irradiation, reported[19] to accelerate solution-phase Baylis−Hillman reactions, was also not profitable in our solid-phase work. The addition[9b] of lanthanum(III) trifluoromethanesulfonate as a Lewis acid was found to be beneficial. The original report used acetonitrile as solvent, which was inferior to DMF in polymer swelling. However, in solution phase, we found the catalyst to be less effective with neat DMF. Thus, we used a 3:1 DMF/acetonitrile mixture for our solid-phase reactions. Meanwhile, after our work was completed, the Jung group published[11b] a study of solvent effects on non-lanthanide accelerated solid-phase Baylis−Hillman reactions, in which 1:1 $CHCl_3$/DMSO gave the best yield.

With optimized conditions in hand, we carried out these reactions with a series of aldehydes and aryl bromides (Scheme 5). Besides the desired aryl ketone **1**, the major byproduct was a much more polar fraction that was identified as the corresponding cinnamic acid, resulting from Heck arylation of unreacted acrylate on the resin. Overall yields of isolated product (Table 2) appear low but are reasonable for the combination of Baylis−Hillman and Heck reactions followed by resin cleavage. As the solution-phase Heck arylation precedents[15] proceed fairly efficiently in 67−86% yield, we believe our yields are largely determined by the Baylis−Hillman reactions. Previous solid-phase examples[11] have also noted the problem of incomplete reaction for this transformation. Finally, aliphatic aldehydes were found to be poorer Baylis−Hillman substrates, as in solution phase.

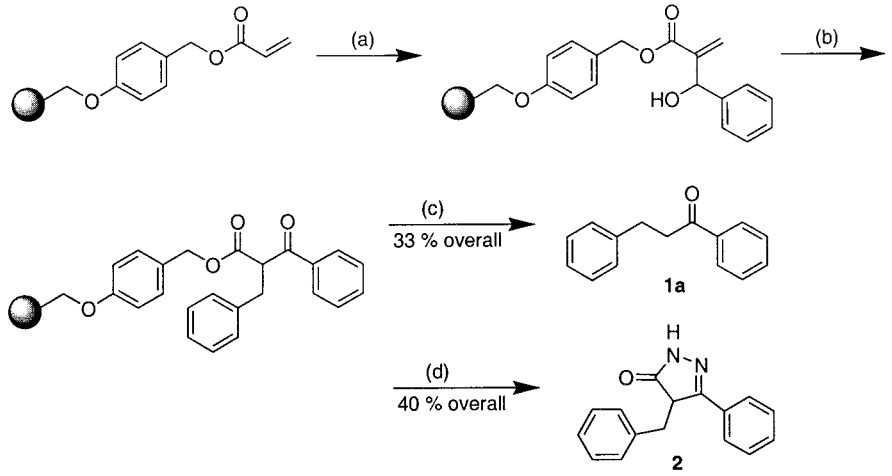
Conclusions

Our initial goal was to establish the scope of the solid-phase Baylis−Hillman reaction with a variety of aldehydes. Yields were monitored following a subsequent Heck arylation and decarboxylative resin cleavage. Although quantitative yields are unlikely for two consecutive carbon−carbon bond forming reactions, the overall efficiency of this three-step process is relatively modest.

The deficiencies in this reaction sequence are mainly due to incomplete Baylis−Hillman reaction. With hindsight, this is not surprising as solution-phase Baylis−Hillman reactions are often carried out with neat acrylate as solvent over extended reaction times. Thus, the ability to use large reagent excesses or repeat reactions on solid phase does not result in significant improvement. Furthermore, the reaction is rather capricious in terms of suitable aldehydes. Among the aromatic aldehydes, both electron-poor and electron-rich examples are capable of giving low yields (Table 2), while the aliphatic cases tested were generally poor (except for formaldehyde).

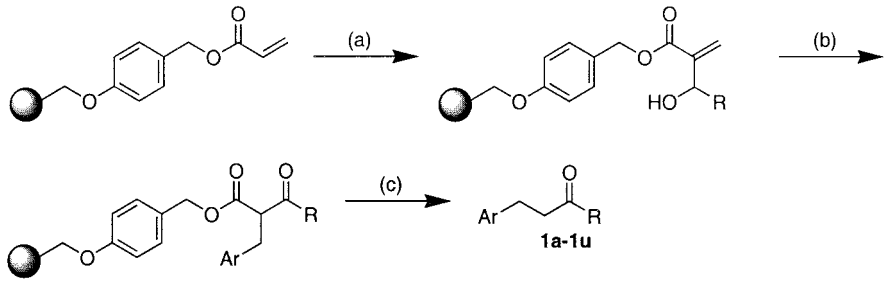
A second objective was to parlay the Baylis−Hillman products into scaffolds of pharmacological interest. We chose two targets, monocylic β-lactams or azetidines and β-keto esters, which in turn are precursors to various heterocycles. Unfortunately, the low overall yields disfavor the Baylis−Hillman route compared to other approaches to such compounds. While the Baylis−Hillman reaction does provide

Scheme 4[a]



[a] Reagents and conditions: (a) PhCHO (20 equiv), DABCO (20 equiv), $La(OTf)_3$ (1 equiv), 3:1 DMF/CH_3CN, 24 h; (b) C_6H_5Br (16 equiv), $Pd(OAc)_2$ (0.5 equiv), $NaHCO_3$ (40 equiv), Bu_4NBr (8 equiv), THF reflux, 10 h; (c) 75% TFA:CH_2Cl_2, 1 h; (d) $NH_2NH_2 \cdot H_2O$ (10 equiv), THF, 16 h.

Scheme 5[a]



[a] Reagents and conditions: (a) RCHO (20 equiv), DABCO (20 equiv), $La(OTf)_3$ (1 equiv), 3:1 DMF/CH_3CN, 4 days; (b) ArBr (10 equiv), $Pd_2(dba)_3$ (0.33 equiv), P(*o*-Tol)$_3$ (0.66 equiv), Et_3N (10 equiv), DMF, 100 °C, 24 h; (c) 75% TFA/CH_2Cl_2, 1 h.

Table 1. Influence of Baylis−Hillman Reaction Parameters on Yield of **1a**

reaction time	additive[a]	yield (%)[b]
24 h	none	33
2 × 24 h	none	38
7 days	none	43
15 days	none	43
microwave, 1 × 10 min[c]	none	5
microwave, 1 × 20 min	none	6
8 h	$La(OTf)_3$	29
24 h	$La(OTf)_3$	36
2 × 2 days	$La(OTf)_3$	45
4 days	$La(OTf)_3$	49
7 days	$La(OTf)_3$	47
microwave, 1 × 10 min	$La(OTf)_3$	4
microwave, 1 × 20 min	$La(OTf)_3$	5

[a] Baylis−Hillman reactions with 1 equiv of $La(OTf)_3$ were performed in 3:1 DMF/CH_3CN, others in neat DMF. [b] Isolated yields after preparative TLC, based on capacity of polystyrene−Wang resin. [c] Microwave reactions were carried out by 1 min irradiations at 30 W with cooling to room temperature in between.

highly functional molecules, the inherent limitations suggest that it is best used with particularly reactive substrates rather than a general diversification strategy employing a broad range of aldehydes.

Experimental Section

General. All chemicals obtained commercially were used without further purification. Dichloromethane was distilled from CaH_2 immediately before use. Polystyrene−Wang resin (capacity: 1.08 mmol/g) was obtained from Calbiochem-Novabiochem. Analytical TLC was performed on precoated glass plates (Merck, silica gel 60F-254) and visualized under UV light. Preparative TLC was carried out on 20 × 20 cm glass plates precoated with 1 mm silica gel (Aldrich). ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$ solutions on a Bruker Avance-400 instrument. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Mass spectra were obtained on a Perkin-Elmer API-300 operating in ESI mode.

Loading of Acrylic Acid. Polystyrene−Wang resin (2.0 g, 2.16 mmol) was suspended in CH_2Cl_2 (50 mL) and cooled to 0 °C, followed by the addition of triethylamine (1.0 mL, 3.5 equiv) and acryloyl chloride (526 μL, 3.0 equiv). The reaction mixture was brought to room temperature, agitated for 3 h, and filtered, and the resin was washed [DMF, MeOH, CH_2Cl_2 (3 × 25 mL each)] and dried. The above reaction was repeated once more with fresh reagents.

Baylis−Hillman Reactions. The acrylate resin (100−200 mg) was suspended in a mixture of DMF (1.5 mL) and CH_3CN (0.5 mL), followed by the addition of 1,4-diazabicyclo[2.2.2]octane [DABCO] (20 equiv), aldehyde (20 equiv), and lanthanum(III) trifluoromethanesulfonate (1 equiv). After the mixture was agitated for 4 days, the resin was filtered, washed [DMF, MeOH, CH_2Cl_2 (3 × 20 mL each)], and dried.

Heck Reactions. The above resin was suspended in DMF

Table 2. Examples of Sequential Baylis−Hillman and Heck Reactions

compd	R	Ar	yield[a] (%)
1a	Ph	Ph	49
1b	Ph	4-(NH_2)Ph	30
1c	Ph	4-(OH)Ph[b]	29
1d	Ph	3-(OMe)Ph	29
1e	Ph	2-(NO_2)-4-MePh	38
1f	Ph	3-pyridyl	45
1g	2-MePh	Ph	30
1h	2-MePh	2-(NO_2)-4-MePh	25
1i	2,4-Me_2Ph	3-(OMe)Ph	2
1j	4-(Ph)Ph	Ph	35
1k	4-(OMe)Ph	Ph	22
1l	4-(CN)Ph	Ph	30
1m	4-(CN)Ph	3-(OMe)Ph	30
1n	2-(NO_2)Ph	2-(NO_2)Ph	15
1o	4-(NO_2)Ph	Ph	25
1p	4-(NO_2)Ph	4-(OH)Ph[b]	14
1q	4-(NO_2)Ph	3-(OMe)Ph	18
1r	4-(NO_2)Ph	3-pyridyl	26
1s	4-(NO_2)Ph	2-(NO_2)-4-MePh	28
	4-imidazolyl	Ph	0[c]
	n-C_5H_{11}	Ph	nd[d]
1t	*n*-C_5H_{11}	4-(OH)Ph[b]	6
	isoamyl	Ph	0[c]
	isoamyl	3-pyridyl	0[c]
	cyclohexyl	3-(OMe)Ph	nd[d]
1u	cyclohexyl	2-(NO_2)-4-MePh	4

[a] Based on manufacturer's loading of polystyrene−Wang resin. [b] In this case, we used 4-iodophenol rather than 4-bromophenol. [c] The desired ketone was not observed in NMR spectra of the crude resin cleavage mixture. [d] Not determined: the product could not be separated from impurities.

(5 mL) and triethylamine (10 equiv) followed by the addition of tri-*o*-tolylphosphine [P(*o*-tolyl)$_3$] (0.66 equiv), tris(dibenzylidene acetone) dipalladium(0) [$Pd_2(dba)_3$] (0.33 equiv), and aryl halide (10 equiv). The reaction mixture was stirred at 100 °C for 24 h under an inert atmosphere. The resin was filtered, washed [DMF, MeOH, CH_2Cl_2 (3 × 20 mL each)], and dried. Product cleavage was accomplished by suspending the resin in 75% TFA:CH_2Cl_2 (3 mL) and agitating for 1 h. After the mixture was filtered and washed with CH_2Cl_2 (10 × 3 mL), the combined filtrates were concentrated and purified by preparative TLC using 10−20% EtOAc:hexanes (with 1% CH_2Cl_2 or MeOH for more polar compounds) as eluent to yield the pure aryl ketone.

1-Propanone, 1,3-Diphenyl- (1a): ^{1}H NMR δ 3.09 (t, J = 7.5 Hz, 2H), 3.32 (t, J = 7.4 Hz, 2H), 7.22−7.34 (m, 5H), 7.47 (t, J = 7.5 Hz, 2H), 7.56 (d, J = 7.3 Hz, 1H), 7.97 (d, J = 7.4 Hz, 2H); ^{13}C NMR δ 30.1, 40.5, 126.2, 128.1, 128.4, 128.5, 128.6, 133.1, 136.9, 141.3, 199.3; MS m/z 211 $(M + 1)^+$.

1-Propanone, 1-Phenyl-3-(4-aminophenyl)- (1b): ^{1}H NMR δ 2.97 (t, J = 7.3 Hz, 2H), 3.26 (t, J = 7.3 Hz, 2H), 6.65 (d, J = 8.2 Hz, 2H), 7.05 (d, J = 8.2 Hz, 2H), 7.46 (t, J = 7.4 Hz, 2H), 7.56 (d, J = 7.2 Hz, 1H), 7.97 (d, J = 7.4 Hz, 2H); ^{13}C NMR δ 29.4, 40.9, 115.4, 128.1, 128.6, 129.2, 131.3, 133.0, 136.9, 144.5, 199.7; MS m/z 226 $(M + 1)^+$.

1-Propanone, 1-Phenyl-3-(4-hydroxyphenyl)- (1c): ^{1}H NMR δ 3.01 (t, J = 7.4 Hz, 2H), 3.28 (t, J = 7.3 Hz, 2H), 4.75 (br s, 1H), 6.78 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 7.46 (t, J = 7.4 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.97 (d, J = 7.4 Hz, 2H); ^{13}C NMR δ 29.3, 40.7, 115.3, 128.1, 128.6, 129.6, 133.1, 133.4, 136.9, 153.9, 199.6; MS m/z 227 $(M + 1)^+$.

1-Propanone, 1-Phenyl-3-(3-methoxyphenyl)- (1d): ^{1}H NMR δ 3.06 (t, J = 7.5 Hz, 2H), 3.32 (t, J = 7.4 Hz, 2H), 3.81 (s, 3H), 6.78−6.87 (m, 3H), 7.23−7.27 (m, 1H), 7.47 (t, J = 7.5 Hz, 2H), 7.57 (s, 1H), 7.97 (d, J = 7.5 Hz, 2H); ^{13}C NMR δ 30.1, 40.4, 55.2, 111.4, 114.2, 120.8, 128.1, 128.6, 129.5, 133.1, 136.8, 142.9, 159.7, 199.2; MS m/z 241 $(M + 1)^+$.

1-Propanone, 1-Phenyl-3-(2-nitro-4-methylphenyl)- (1e): ^{1}H NMR δ 2.41 (s, 3H), 3.29 (t, J = 7.0 Hz, 2H), 3.39 (t, J = 6.8 Hz, 2H), 7.36 (d, J = 7.5 Hz, 2H), 7.44−7.48 (m, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.78 (s, 1H), 7.97 (d, J = 7.4 Hz, 2H); ^{13}C NMR δ 20.7, 27.5, 39.5, 125.2, 128.1, 128.6, 132.4, 133.2, 133.5, 134.1, 136.6, 137.8, 149.1, 198.7; MS m/z 270 $(M + 1)^+$.

1-Propanone, 1-Phenyl-3-(3-pyridyl)- (1f): ^{1}H NMR δ 3.09 (t, J = 7.4 Hz, 2H), 3.33 (t, J = 7.5 Hz, 2H), 7.22−7.27 (m, 1H), 7.45−7.61 (m, 4H), 7.96 (d, J = 7.5 Hz, 2H), 8.47 (s, 1H), 8.54 (s, 1H); ^{13}C NMR δ 27.1, 39.8, 123.4, 128.0, 128.1, 128.7, 133.3, 136.2, 136.6, 147.6, 149.9, 198.5; MS m/z 212 $(M + 1)^+$.

1-Propanone, 1-(2-Methylphenyl)-3-phenyl- (1g): ^{1}H NMR δ 2.48 (s, 3H), 3.05 (t, J = 7.4 Hz, 2H), 3.24 (t, J = 7.3 Hz, 2H), 7.21−7.37 (m, 8H), 7.61 (d, J = 7.4 Hz, 1H); ^{13}C NMR δ 21.3, 30.3, 43.2, 125.7, 126.1, 128.4, 128.4, 128.5, 131.3, 132.0, 137.9, 138.1, 141.2, 203.4; MS m/z 225 $(M + 1)^+$.

1-Propanone, 1-(2-Methylphenyl)-3-(2-nitro-4-methylphenyl)- (1h): ^{1}H NMR δ 2.41 (s, 3H), 2.50 (s, 3H), 3.27−3.32 (m, 4H), 7.24−7.38 (m, 5H), 7.64 (d, J = 7.3 Hz, 1H), 7.77 (s, 1H); ^{13}C NMR δ 20.7, 21.4, 27.6, 42.2, 125.2, 125.7, 128.6, 131.4, 132.0, 132.3, 133.5, 134.1, 137.5, 137.8, 138.2, 149.1, 202.6; MS m/z 284 $(M + 1)^+$.

1-Propanone, 1-(2,4-Dimethylphenyl)-3-(3-methoxyphenyl)- (1i): ^{1}H NMR δ 2.36 (s, 3H), 2.49 (s, 3H), 3.02 (t, J = 7.9 Hz, 2H), 3.22 (t, J = 7.3 Hz, 2H), 3.80 (s, 3H), 6.76−6.84 (m, 2H), 7.04−7.06 (m, 2H), 7.41−7.42 (m, 1H), 7.78 (m, 1H), 7.96 (m, 1H); ^{13}C NMR δ 21.6, 21.6, 30.5, 42.8, 55.2, 111.4, 114.2, 120.8, 126.3, 127.4, 128.4, 129.0, 129.0, 129.5, 132.9, 141.9, 159.7, 198.7; MS m/z 269 $(M + 1)^+$.

1-Propanone, 1-(Biphenyl)-3-phenyl- (1j): ^{1}H NMR δ 3.11 (t, J = 7.5 Hz, 2H), 3.36 (t, J = 7.4 Hz, 2H), 7.23−7.50 (m, 8H), 7.63 (d, J = 7.6 Hz, 2H), 7.69 (d, J = 8.2 Hz, 2H), 8.05 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 30.2, 40.5, 126.2, 127.2, 127.3, 128.2, 128.5, 128.6, 128.7, 129.0, 135.5, 139.9, 141.3, 145.8, 198.9; MS m/z 287 $(M + 1)^+$.

1-Propanone, 1-(4-Methoxyphenyl)-3-phenyl- (1k): ^{1}H NMR δ 3.07 (t, J = 7.5 Hz, 2H), 3.26 (t, J = 7.4 Hz, 2H), 3.88 (s, 3H), 6.94 (d, J = 8.7 Hz, 2H), 7.21−7.33 (m, 5H), 7.96 (d, J = 8.7 Hz, 2H); ^{13}C NMR δ 30.3, 40.1, 55.5, 113.7, 126.1, 128.4, 128.5, 130.0, 130.3, 141.5, 163.5, 197.9; MS m/z 241 $(M + 1)^+$.

1-Propanone, 1-(4-Cyanophenyl)-3-phenyl- (1l): ^{1}H NMR δ 3.09 (t, J = 7.4 Hz, 2H), 3.33 (t, J = 7.4 Hz, 2H), 7.23−7.33 (m, 5H), 7.77 (d, J = 8.2 Hz, 2H), 8.04 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 29.9, 40.8, 116.4, 117.9, 126.4, 128.4, 128.5, 128.7, 132.5, 139.8, 140.7, 197.8; MS m/z 236 $(M + 1)^+$.

1-Propanone, 1-(4-Cyanophenyl)-3-(3-methoxyphenyl)-(1m): ^{1}H NMR δ 3.06 (t, J = 7.4 Hz, 2H), 3.32 (t, J = 7.3 Hz, 2H), 3.81 (s, 3H), 6.77−6.85 (m, 3H), 7.21−7.27 (m, 1H), 7.77 (d, J = 8.3 Hz, 2H), 8.04 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 29.9, 40.7, 55.2, 111.5, 114.3, 116.4, 117.9, 120.7, 128.4, 129.6, 132.5, 139.7, 142.3, 159.8, 197.8; MS m/z 266 $(M + 1)^+$.

1-Propanone, 1-(2-Nitrophenyl)-3-(2-nitrophenyl)-(1n): ^{1}H NMR δ 3.22 (t, J = 7.5 Hz, 2H), 3.40 (t, J = 7.5 Hz, 2H), 7.40 (d, J = 6.3 Hz, 2H), 7.42−7.61 (m, 3H), 7.72 (d, J = 7.3 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 8.14 (d, J = 8.0 Hz, 1H); ^{13}C NMR δ 27.8, 43.6, 124.5, 125.0, 127.3, 127.7, 129.0, 130.0, 130.6, 132.8, 133.4, 134.4, 135.8, 137.7, 200.9; MS m/z 301 $(M + 1)^+$.

1-Propanone, 1-(4-Nitrophenyl)-3-phenyl- (1o): ^{1}H NMR δ 3.11 (t, J = 7.4 Hz, 2H), 3.36 (t, J = 7.6 Hz, 2H), 7.24−7.34 (m, 5H), 8.11 (d, J = 8.7 Hz, 2H), 8.31 (d, J = 8.7 Hz, 2H); ^{13}C NMR δ 29.9, 41.0, 120.8, 123.9, 126.4, 128.4, 128.7, 129.0, 140.6, 141.2, 197.6; MS m/z 256 $(M + 1)^+$.

1-Propanone, 1-(4-Nitrophenyl)-3-(4-hydroxyphenyl)-(1p): ^{1}H NMR δ 3.03 (t, J = 7.4 Hz, 2H), 3.32 (t, J = 7.6 Hz, 2H), 6.78 (d, J = 8.3 Hz, 2H), 7.12 (d, J = 8.3 Hz, 2H), 8.09 (d, J = 8.8 Hz, 2H), 8.31 (d, J = 8.7 Hz, 2H); ^{13}C NMR δ 29.0, 41.3, 115.4, 123.9, 129.1, 129.6, 130.5, 132.7, 141.3, 154.1, 197.8. MS m/z 272 $(M + 1)^+$.

1-Propanone, 1-(4-Nitrophenyl)-3-(3-methoxyphenyl)-(1q): ^{1}H NMR δ 3.07 (t, J = 7.4 Hz, 2H), 3.36 (t, J = 7.7 Hz, 2H), 3.80 (s, 3H), 6.76−6.85 (m, 2H), 7.21−7.26 (m, 2H), 8.09 (d, J = 8.7 Hz, 2H), 8.30 (d, J = 8.7 Hz, 2H); ^{13}C NMR δ 29.9, 40.9, 55.2, 111.5, 114.4, 120.7, 123.9, 129.0, 129.7, 141.2, 142.2, 150.3, 159.8, 197.6; MS m/z 284 $(M - 1)^+$.

1-Propanone, 1-(4-Nitrophenyl)-3-(3-pyridyl)- (1r): ^{1}H NMR δ 3.13 (t, J = 7.2 Hz, 2H), 3.38 (t, J = 7.2 Hz, 2H), 7.27 (m, 1H), 7.61 (d, J = 7.6 Hz, 1H), 8.11 (d, J = 8.3 Hz, 2H), 8.32 (d, J = 8.3 Hz, 2H), 8.50−8.56 (m, 2H); ^{13}C NMR δ 26.8, 40.4, 124.0, 128.9, 129.0, 136.2, 140.9, 145.0, 147.8, 149.8, 150.4, 196.8; MS m/z 257 $(M + 1)^+$.

1-Propanone, 1-(4-Nitrophenyl)-3-(2-nitro-4-methylphenyl)- (1s): ^{1}H NMR δ 2.42 (s, 3H), 3.31 (t, J = 7.2 Hz, 2H), 3.44 (t, J = 7.3 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.81 (s, 1H), 8.13 (d, J = 8.7 Hz, 2H), 8.32 (d, J = 8.7 Hz, 2H); ^{13}C NMR δ 20.8, 27.4, 40.2, 123.9, 124.0, 125.3, 129.1, 132.5, 132.8, 134.3, 138.2, 141.0, 150.4, 197.2; MS m/z 315 $(M + 1)^+$.

3-Octanone-1-(4-hydroxyphenyl)- (1t): ^{1}H NMR δ 0.88 (t, J = 7.2 Hz, 3H), 1.59 (m, 6H), 2.37 (t, J = 7.4 Hz, 2H), 2.71 (t, J = 7.4 Hz, 2H), 2.83 (t, J = 7.4 Hz, 2H), 6.75 (d, J = 8.3 Hz, 2H), 7.05 (d, J = 8.3 Hz, 2H); ^{13}C NMR δ 13.9, 22.4, 23.5, 28.9, 31.4, 43.1, 44.5, 115.2, 129.5, 133.4, 153.8, 210.6; MS m/z 221 $(M + 1)^+$.

1-Propanone, 1-Cyclohexane-3-(2-nitro-4-methylphenyl)- (1u): ^{1}H NMR δ 1.22−1.33 (m, 6H), 1.66−1.83 (m, 4H), 2.11 (m, 1H), 2.40 (s, 3H), 2.82 (t, J = 7.3 Hz, 2H), 3.09 (t, J = 7.4 Hz, 2H), 7.26−7.33 (m, 2H), 7.75 (s, 1H); ^{13}C NMR δ 20.7, 25.6, 25.8, 27.0, 28.4, 29.7, 41.2, 50.9, 53.4, 125.1, 132.3, 133.6, 134.0, 137.6, 149.1, 198.9; MS m/z 276 $(M + 1)^+$.

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Supporting Information Available. ^{1}H NMR spectra of compounds **1a**−**h,j,l**−**o,q,s**. This material is available free of charge via the Internet at http://pubs.acs.org.

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