Bismuth(III) Oxychloride Procatalyst Based One-Pot Multicomponent Synthesis of β′-Acetamido-β-dicarbonyl Compounds with Special Reference to *pref*-β′-Acetamido-β-oxo Esters

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Abstract: Bismuth(III) chloride generated in situ from the procatalyst bismuth(III) oxychloride and acetyl chloride efficiently catalyzes the one-pot synthesis of β′-acetamido-β-dicarbonyl compounds from aldehydes, enolizable β-diketones, or β-oxo esters and acetyl chloride in acetonitrile solution and under solvent-free conditions at room temperature; in the case of the β-oxo ester derived products, these are obtained with moderate to excellent diastereoselectivity in favor of the *pref*-isomer. X-ray crystallographic analysis of one *pref*-β′-acetamido-β-oxo ester exhibits C–H···O and N–H···O intermolecular interactions in the three-dimensional supramolecular assembly.

Key words: multicomponent reaction, bismuth(III) oxychloride, bismuth(III) chloride, catalysis, β′-acetamido-β-dicarbonyl compounds, diastereoselectivity

One-pot multicomponent synthesis has drawn the attention of many organic chemists because of the advantages it has over conventional multistep synthesis and the potential for its application to the generation of library compounds for drug development.[1] β-Amino alcohols derived from β-acetamido ketones are important structural units common in naturally occurring nucleoside antibiotics, e.g. nikkomycins or neopolyoxins.[2] β-Acetamido esters are readily converted into β-amino acids, which are important synthons for the generation of structural scaffolds related to peptidomimetic enzyme inhibitors of current interest.[3]

Reported Lewis acid catalyzed one-pot syntheses of β-acetamido carbonyl compounds are based on cobalt(II) chloride,[4a–c] poly-cobalt(II) chloride,[4d] montmorillonite K10,[4e] silica gel–sulfuric acid,[4f] or bismuth(III) oxychloride.[5] Methods based on cobalt(II) chloride or montmorillonite K10 generate mainly the *parf*-β′-acetamido-β-oxo esters (described as *anti*-isomer by Iqbal[4a–d]) from the corresponding β-oxo esters. Recently, bismuth(III) salts have gained much attention in organic synthesis.[6] In an earlier report[5] we showed that bismuth(III) chloride generated in situ from the procatalyst bismuth(III) oxychloride efficiently catalyzed the one-pot synthesis of β-acetamido ketones starting from the corresponding aromatic aldehyde, an enolizable ketone, acetonitrile, and acetyl chloride. In continuation of our research on bismuth(III) oxychloride based organic synthesis,[5,6l,m] we report herein, the efficient application of this reagent in the one-pot synthesis, in solution as well as under solvent-free conditions, of β-acetamido carbonyl compounds **4** and **5** derived from enolizable β-dicarbonyl starting materials **2** and **3**, with special reference to the corresponding *pref*-β′-acetamido-β-oxo esters **4** (Table 1), which could be utilized as structural units for the generation of corresponding peptidomimetic library compounds.

Under optimized conditions, benzaldehyde (**1a**) reacted with methyl acetoacetate (**2**) and acetyl chloride in acetonitrile (reagent as well as solvent) in the presence of bismuth(III) oxychloride (20 mol%) at room temperature to give the corresponding β′-acetamido-β-oxo ester **4a** in 96% yield and with moderate diastereoselectivity (3:1) in favor of the *pref*-isomer (Table 1, entry 1). Under similar condition, aromatic aldehydes **1c–g** containing electron-donating groups like chloro, methyl, hydroxy, bromo, or fluoro in the aromatic ring (Table 1, entries 5, 6, 8–10) reacted with methyl acetoacetate (**2**), acetyl chloride, and acetonitrile in acetonitrile solution producing quite efficiently the corresponding products **4c–g**; concomitant acetylation of the 4-hydroxy group of **1e** occurred to give **4e**. The *pref*-selectivities of the products **4c–e**,**g** (Table 1, entries 5, 6, 8, and 10) were excellent, but the bromo-substituted product **4f** (Table 1, entry 9) did not show any stereoselectivity in solution. Although, the yields of the products from aromatic aldehydes containing electron-withdrawing groups like nitro or cyano in the ring **1b** or **1h** were good with moderate *pref*-selectivity of the nitro-substituted product **4b** (Table 1, entry 4), the 4-cyanobenzaldehyde derived product **4h** exhibited no stereoselectivity in solution (Table 1, entry 11). The reactions of all these substrates **1a–h** proceed efficiently under solvent-free condition at ambient temperature with overall excellent or exclusive *pref*-selectivity of most of the products (Table 1, entries 1, 4–6, 8–10). Although, the selectivity of the 4-cyanobenzaldehyde (**1h**) reaction under solvent-free conditions was moderate (1:2.7), it was only 1:1 when acetonitrile was used as the reactant and solvent (Table 1, entry 11). It is interesting to note that the diastereoselectivity of the 4-nitrobenzaldehyde (**1b**) reactions changed dramatically from *parf*/*pref* 1:4 (MeCN as solvent) to exclusively *pref* (solvent-free) and for 4-bromobenzaldehyde (**1f**) reactions *parf*/*pref* 1:1 (MeCN as

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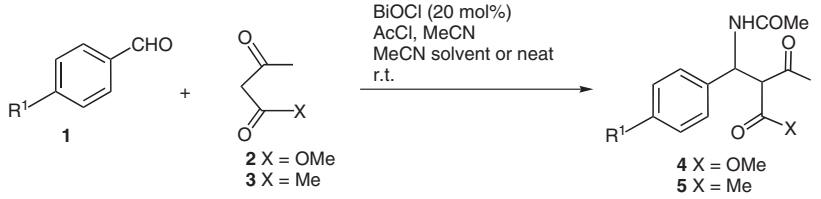
Table 1 Bismuth(III) Oxychloride Procatalyst Based One-Pot Synthesis of β′-Acetamido-β-dicarbonyl Compounds



Entry	Aldehyde	β′-Acetamido-β-dicarbonyl compound			Time (h) soln [neat]	Yield[a] (%) soln [neat]	Ratio[b] *parf*/*pref* solution [neat]
			R	X			
1	**1a**	**4a**	Ph	OMe	6 [7]	96 [93]	1:3 [1:5.7]
2	**1a**	**4a**	Ph	OMe	6 [7]	91[c] [92]	1:3 [1:6.6]
3	**1a**	**4a**	Ph	OMe	6 [–[d]]	90[e] [–[d]]	1:3 [–[d]]
4	**1b**	**4b**	4-$O_2NC_6H_4$	OMe	12 [12]	58 [57]	1:4 [*pref* only]
5	**1c**	**4c**	4-ClC_6H_4	OMe	12 [12]	75 [76]	1:27 [1:15]
6	**1d**	**4d**	4-MeC_6H_4	OMe	5 [5]	82 [82]	*pref* only [*pref* only]
7	**1d**	**4d**	4-MeC_6H_4	OMe	4 [–[d]]	85[f] [–[d]]	1:3 [–[d]]
8	**1e**[g]	**4e**	4-$AcOC_6H_4$	OMe	24 [28]	61 [53]	1:7.5 [1:7.5]
9	**1f**	**4f**	4-BrC_6H_4	OMe	22 [27]	87 [81]	1:1 [1:11]
10	**1g**	**4g**	4-FC_6H_4	OMe	10 [15]	87 [84]	1:6.6 [1:10]
11	**1h**	**4h**	4-NCC_6H_4	OMe	22 [28]	75 [65]	1:1 [1:2.7]
12	**1a**	**5a**	Ph	Me	4 [6]	91 [91]	–
13	**1b**	**5b**	4-$O_2NC_6H_4$	Me	12 [12]	57 [53]	–
14	**1c**	**5c**	4-ClC_6H_4	Me	4 [4]	90 [89]	–
15	**1d**	**5d**	4-MeC_6H_4	Me	10 [10]	70 [68]	–
16	**1e**[g]	**5e**	4-$AcOC_6H_4$	Me	12 [12]	89 [85]	–
17	**1h**	**5h**	4-NCC_6H_4	Me	8 [11]	92 [90]	–
18	**1i**	**5i**	4-$MeOC_6H_4$	Me	14 [14]	61 [62]	–
19	**1j**	**5j**	*n*-C_7H_{15}	Me	14 [18]	85 [92]	–

[a] Unoptimized chromatographed yields.
[b] By ^1H NMR.
[c] Scale-up experiment (~ ten-fold).
[d] Reaction not performed.
[e] The reaction was performed with recovered BiOCl (~ ten-fold).
[f] At 50 °C.
[g] Starting from **1e**, R = 4-HOC_6H_4.

solvent) to 1:11 (solvent-free); the reason for the dramatic change in selectivity in these substrates which have the opposite electron demand is not, however, clear. It is interesting to note that the overall diastereoselectivities of the β′-acetamido-β-oxo esters **4a**–**h** from the bismuth(III) oxychloride based one-pot reaction differed from those observed by Iqbal et al. in the cobalt(II) chloride or montmorillonite K10 catalyzed one-pot reactions,[4] the latter proceeded mainly with *parf*-selectivity. The *pref*-selectivity of the present reactions was established by NMR of the products and finally confirmed by the X-ray crystallographic analysis[7] of the single crystal of a model compound **4d** (ORTEP diagram in Figure 1). Crystal packing exhibited intermolecular N–H···O and C–H···O hydrogen bonds between molecules related by translation to form infinite chains of $R_2^2(14)$ rings propagating along the [010] direction. Additional intermolecular C–H···O hydrogen bonds in the [101] direction between molecules related by the screw symmetry link the parallel chains into three-dimensional supramolecular assembly (Figure 2).

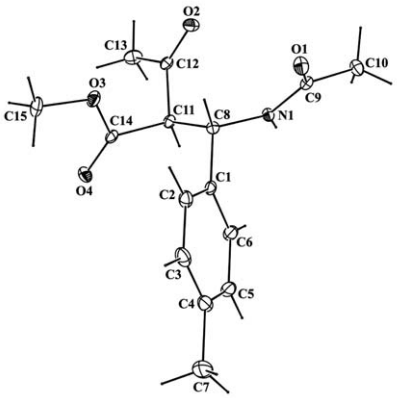


Figure 1 ORTEP structure of *pref*-**4d**

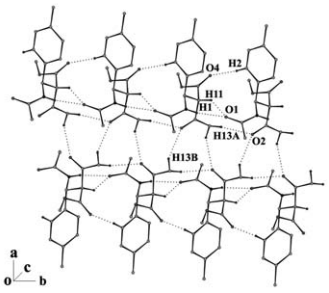


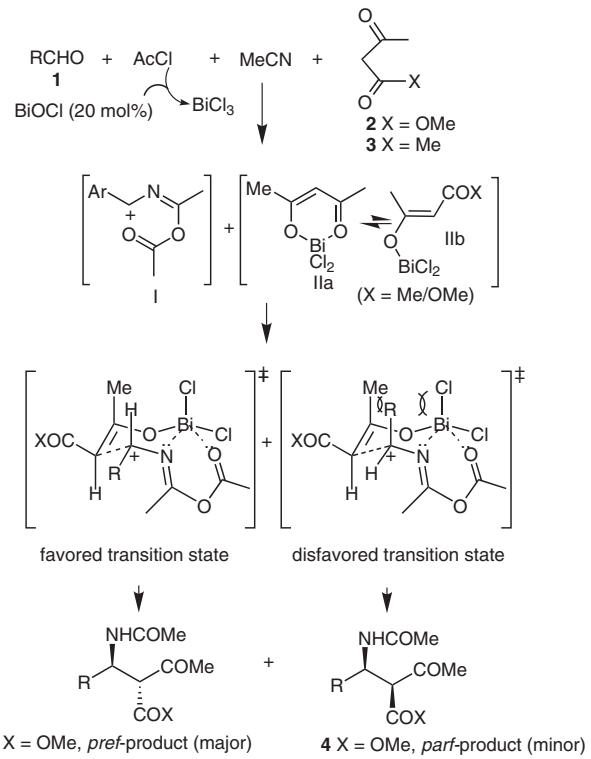
Figure 2 Crystal packing of *pref*-**4d**

The efficacies of the one-pot syntheses of β′-acetamido-β-dicarbonyl compounds from benzaldehyde (**1**) or its deactivated or activated derivatives **1b**,**d**,**f** catalyzed by other bismuth(III) salts (20 mol% each) namely bismuth(III) triflate, bismuth(III) bromide, bismuth sulfate, or bismuth subnitrate and also by the Brönsted acid hydrochloric acid were compared with those of the corresponding bismuth(III) oxychloride based reactions. The results of these reactions are summarized in Table 2.

Under standard reaction condition, the yields of the reactions of the substrates, benzaldehyde (**1a**), 4-nitrobenzaldehyde (**1b**) or 4-tolualdehyde (**1d**), in acetonitrile solution or under solvent-free conditions based on bismuth(III) oxychloride were better in comparison with the reactions based on bismuth(III) triflate, bismuth(III) bromide, bismuth sulfate, or bismuth subnitrate (cf. Table 1, entries 1, 4, 7 and Table 2). The *pref*-selectivities of the reactions from benzaldehyde (**1a**), 4-nitrobenzaldehyde (**1b**), or 4-tolualdehyde (**1d**) in solution based on other bismuth(III) salts were comparable in a few cases (Table 1, entry 1, vs Table 2, entries 1, 5, 9, and 13 and Table 1, entry 4 vs Table 2 entries 6 and 14), better on two occasions (Table 1, entry 4 vs Table 2, entries 2 and 10) or much lower in other reactions in solution or under neat conditions with respect to those conducted by bismuth(III) oxychloride. As mentioned earlier, the 4-bromobenzaldehyde (**1f**) derived reaction in the presence of bismuth(III) oxychloride in solution was unselective, although the reaction catalyzed by other bismuth(III) salts showed varied selectivities in favor of the *pref*-diastereomer.

It is worthwhile to mention that the reactions of the substrates **1a**,**b**,**d**,**f** with methyl acetoacetate (**2**) and acetyl chloride in acetonitrile in the presence of the Brønsted acid, hydrochloric acid (20 mol%, Table 2) also produced the corresponding β′-acetamido-β-dicarbonyl compounds **4**, but in lower yields compared to their bismuth(III)-based Lewis acid counterparts. Like the previous cases, the *pref*-selectivities of hydrochloric acid catalyzed reactions in solution, except that from 4-bromobenzaldehyde (**1f**), were lower in comparison with those obtained from reactions conducted in the presence of bismuth(III) oxychloride.

The *pref*-selectivity of the β-oxo ester derived products **4** in the present procedure can be explained by the coupling of the intermediate (**I**, initially generated in situ by the reaction of the aldehyde, acetyl chloride, and acetonitrile) with mainly the β-oxo ester derived bismuth (*E*)-enolate **IIb**, probably via the kinetically more favored six-membered transition state (Scheme 1, shown with bismuth(III) oxychloride, arising out of *Re-Si* or *Si-Re* attack) in which bismuth attains a pentagonal bipyramidal geometry. 1,3-*syn*-Diaxial interactions in the other possible transition state (Scheme 1, arising from *Re-Re* or *Si-Si* attack) make that pathway more energy-demanding, leading to the kinetically less favored *parf*-diastereomer. This is also corroborated by the decrease in *pref*-selectivity in the reaction of 4-tolualdehyde (**1d**) (Table 1, entry 7) at higher temperature. It is worthwhile to mention here that the present synthesis of β′-acetamido-β-oxo esters **4** is highly



Scheme 1

Table 2 Synthesis of β′-Acetamido-β-dicarbonyl Compounds Catalyzed by Bismuth(III) Salts or Hydrochloric Acid (20 mol%)

Entry	Substrate	Catalyst	Time (h) soln [neat]	Product	Yield (%) soln [neat]	Ratio *parf*/*pref*[a] soln [neat]
1	**1a**	$Bi(OTf)_3$	1 [1]	**4a**	91 [83]	1:4.2 [1:4.5]
2	**1b**	$Bi(OTf)_3$	2 [3]	**4b**	84 [77]	1:10.7 [1:9.3]
3	**1d**	$Bi(OTf)_3$	3 [4]	**4d**	83 [83]	1:4.2 [1:4.2]
4	**1f**	$Bi(OTf)_3$	4 [6]	**4f**	81 [72]	1:6.6 [1:4.6]
5	**1a**	$BiBr_3$	3 [5]	**4a**	85 [81]	1:2.5 [1:3.1]
6	**1b**	$BiBr_3$	5 [7]	**4b**	79 [69]	1:5.2 [1:10.1]
7	**1d**	$BiBr_3$	6 [8]	**4d**	87 [78]	1:6.1 [1:2.4]
8	**1f**	$BiBr_3$	9 [12]	**4f**	85 [76]	1:11.4 [1:3.9]
9	**1a**	$Bi_2(SO_4)_3$	2 [5]	**4a**	89 [90]	1:3.1 [1:2.1]
10	**1b**	$Bi_2(SO_4)_3$	8 [11]	**4b**	82 [78]	1:7.2 [1:5.3]
11	**1d**	$Bi_2(SO_4)_3$	8 [10]	**4d**	88 [82]	1:4.5 [1:1.3]
12	**1f**	$Bi_2(SO_4)_3$	9 [12]	**4f**	90 [83]	1:1.6 [1:5.3]
13	**1a**	$BiONO_3$	5 [8]	**4a**	89 [88]	1:5.2 [1:3.0]
14	**1b**	$BiONO_3$	10 [14]	**4b**	83 [76]	1:4.7 [1:3.6]
15	**1d**	$BiONO_3$	5 [7]	**4d**	83 [85]	1:4.9 [1:17.4]
16	**1f**	$BiONO_3$	12 [16]	**4f**	88 [92]	1:3.1 [1:9.1]
17	**1a**	HCl	72 [–]	**4a**	64 [–]	1:4.2 [–]
18	**1b**	HCl	48 [–]	**4b**	51 [–]	1:2.7 [–]
19	**1d**	HCl	24 [–]	**4d**	70 [–]	1:19.6 [–]
20	**1f**	HCl	36 [–]	**4f**	38 [–]	1:6.9 [–]

[a] By ^{1}H NMR.

pref-selective, although the general stereoselectivity of our earlier synthesis of β-acetamido ketones[5] based on bismuth(III) oxychloride was not good.

The *pref*-selectivity of other bismuth(III) Lewis acids and hydrochloric acid based one-pot reactions are also explained by a similar mechanistic pathway and transition state model as depicted for bismuth(III) oxychloride mediated reactions in Scheme 1. Figure 3 represents the probable favored transition state for hydrochloric acid catalyzed reactions.

The preparative efficacy of the procedure was established through scale-up (~ ten-fold) experiments with benzaldehyde (**1a**), methyl acetoacetate (**2**), acetyl chloride, and acetonitrile in the presence of bismuth(III) oxychloride (20 mol%) in solution and under solvent-free conditions, which produced the corresponding β′-acetamido-β-oxo ester **4a** in excellent yields with comparable *pref*-selectivity in solution and slightly increased *pref*-selectivity under neat conditions (Table 1, entry 2). Recovered bismuth(III) oxychloride[5] also worked equally well (Table 1, entry 3) in terms of yield and diastereoselectivity. It is also to be noted here that unlike some of the reported methods[4b,c] the bismuth(III) oxychloride based one-pot synthesis is not susceptible to the presence of oxygen and the reaction does not require several days to go to completion.

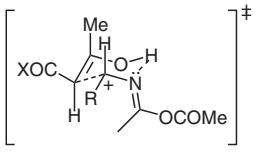


Figure 3 Favored transition state for hydrochloric acid catalyzed reactions

The scope and limitation of the methodology mediated by bismuth(III) oxychloride were further extended by successful one-pot conversion of a mixture of alkyl or aromatic aldehyde, β-diketone, acetyl chloride, and acetonitrile in solution as well as under solvent-free conditions to the corresponding β′-acetamido-β-dioxo compounds **5** in good to excellent yields (Table 1, entries 12–19). It is also to be noted here that for some reasons yet un-

known to us, the reaction of 4-methoxybenzaldehyde (**1i**), acetyl chloride, and acetonitrile with methyl acetoacetate (**2**) in the presence of bismuth(III) oxychloride (20 mol%) in solution did not proceed even though the reaction with acetylacetone (**3**) proceeded to give the desired product **5i** in good yields. Salicylaldehyde was consumed in the reaction mixture with acetyl chloride, acetonitrile, methyl acetoacetate (**2**) and bismuth(III) oxychloride (20 mol%) in solution, but the corresponding product was formed in very poor yield because of the formation of several other side products (not isolated).

In summary, among a variety of bismuth(III) salts, bismuth(III) oxychloride procatalyst-based (bismuth(III) chloride catalyzed) one-pot synthesis describes an efficient method for the generation of *pref*-selective β′-acetamido-β-oxo esters **4** in particular and β′-acetamido-β-dicarbonyl compounds **4** and **5** in general by the one-pot reaction of various aldehydes **1** with methyl acetoacetate (**2**) or acetylacetone (**3**), acetyl chloride, and acetonitrile at room temperature in solution as well as under solvent-free conditions on a milligram or gram scale.

All unknown compounds were characterized by IR, NMR, MS, and elemental analysis. NMR spectra were recorded on Bruker DPX 300 spectrometer using $CDCl_3$ as solvent and TMS as the internal standard. Elemental analyses were performed on a Perkin-Elmer autoanalyzer 2400 II from IACS, Kolkata 700032, India. MS data were taken on GCMS-QP5000 (Shimadzu). The X-ray crystallographic data were recorded on Bruker SMART CCD area detector using graphite monochromator.

All reagents were of commercial grade and were used from freshly opened containers without further purification. Organic solvents were dried by standard methods and were distilled before use. Progress of reactions was checked by TLC on silica gel G (Merck) using EtOAc–petroleum ether (bp 60-80 °C) (2:1) as the mobile phase. Silica gel (60–120 mesh) was used for column chromatography.

β′-Acetamido-β-dicarbonyl Compounds 4 and 5; General Procedure

In solution: To a soln of aldehyde **1** (~1 equiv) and methyl acetoacetate (**2**) or acetylacetone (**3**) (~1 equiv) in anhyd MeCN (4 mL) was added BiOCl (~20 mol%). To the resulting suspension was finally added AcCl (~2 equiv) and the mixture was stirred at r.t. When the reaction was complete, the mixture was diluted with CH_2Cl_2, washed with brine (1 × 20 mL), and the aqueous layer was then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with $NaHCO_3$ soln (1 × 15 mL) followed by H_2O (1 × 20 mL). The organic layer was dried (Na_2SO_4) and concentrated to dryness to give a crude residue that was purified by column chromatography (silica gel, EtOAc–petroleum ether (bp 60–80 °C) (3:2).

Under solvent-free conditions: To a mixture of aldehyde **1** (~1 equiv), methyl acetoacetate (**2**) or acetylacetone (**3**) (~1 equiv), and anhyd MeCN (~3 equiv) was added BiOCl (~20 mol%). Finally, AcCl (~2 equiv) was added and the mixture was stirred at r.t. When the reaction was complete, it was diluted with CH_2Cl_2 (15 mL) and then worked up as described above.

Methyl 3-Acetamido-2-acetyl-3-phenylpropanoate (4a)[4c]

Yield (after chromatography): 96% (soln), 93% (solvent-free).

***pref*-Isomer**

White crystals [EtOAc–petroleum ether (bp 60–80 °C)]; mp 144 °C.

IR (KBr): 3330, 2960, 1745, 1715, 1645, 1530, 1450, 1430, 1365, 1265, 1220, 1160, 1100, 1040, 1000, 905, 840, 760, 705, 620 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.02 (s, 3 H), 2.14 (s, 3 H), 3.71 (s, 3 H), 4.08–4.10 (d, *J* = 5.5 Hz, 1 H), 5.73–5.78 (m, 1 H), 6.90–6.93 (d, *J* = 8.6 Hz, 1 H), 7.24–7.35 (m, 5 H).

Methyl 3-Acetamido-2-acetyl-3-(4-nitrophenyl)propanoate (4b)[4c]

Yield (after chromatography): 58% (soln), 57% (solvent-free).

***pref*-Isomer**

Light yellow crystals [EtOAc–petroleum ether (bp 60–80 °C)]; mp 153–154 °C.

IR (KBr): 3320, 3060, 2980, 2930, 1745, 1710, 1655, 1595, 1545, 1515, 1435, 1345, 1285, 1270, 1230, 1160, 1110, 1040, 960, 910, 860, 805, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.04 (s, 3 H), 2.09 (s, 3 H), 3.34 (s, 3 H), 4.30–4.32 (d, *J* = 4.9 Hz, 1 H), 5.89–5.93 (m, 1 H), 7.09–7.12 (d, *J* = 9.0 Hz, 1 H), 7.45–7.48 (d, *J* = 8.6 Hz, 2 H), 8.17–8.20 (d, *J* = 8.8 Hz, 2 H).

Methyl 3-Acetamido-2-acetyl-3-(4-chlorophenyl)propanoate (4c)[4c]

Yield (after chromatography): 75% (soln), 76% (solvent-free).

***pref*-Isomer**

White crystals [EtOAc–petroleum ether (bp 60–80 °C)]; mp 145 °C.

IR (KBr): 3325, 2960, 2940, 1750, 1715, 1650, 1550, 1435, 1370, 1285, 1270, 1230, 1165, 1120, 1100, 1050, 1020, 910, 850, 725 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.01 (s, 3 H), 2.15 (s, 3 H), 3.73 (s, 3 H), 4.05–4.07 (d, *J* = 5.4 Hz, 1 H), 5.68–5.73 (m, 1 H), 6.92–6.95 (d, *J* = 8.9 Hz, 1 H), 7.21–7.31 (m, 4 H).

Methyl 3-Acetamido-2-acetyl-3-(4-methylphenyl)propanoate (4d)[4c]

Yield (after chromatography): 82% (soln), 82% (solvent-free).

***pref*-Isomer**

White crystals [EtOAc–petroleum ether (bp 60–80 °C)]; mp 130 °C.

IR (KBr): 3330, 3030, 2950, 2920, 1740, 1720, 1645, 1525, 1430, 1370, 1290, 1265, 1220, 1160, 1115, 1090, 1040, 1005, 965, 905, 840, 810, 770, 720, 595 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.99 (s, 3 H), 2.15 (s, 3 H), 2.35 (s, 3 H), 3.70 (s, 3 H), 4.06–4.08 (d, *J* = 5.8 Hz, 1 H), 5.69–5.75 (m, 1 H), 6.87–6.89 (d, *J* = 8.2 Hz, exchangeable NH), 7.10–7.18 (m, 4 H).

^1H NMR (300 MHz, $CDCl_3$, D_2O-exchange): δ = 1.99 (s, 3 H), 2.15 (s, 3 H), 2.3 (s, 3 H), 3.7 (s, 3 H), 4.06–4.08 (d, *J* = 5.9 Hz, 1 H), 5.70–5.72 (d, *J* = 5.8 Hz, 1 H), 7.1–7.18 (m, 4 H).

MS (EI): *m*/*z* = 277 (M^+), 245, 234, 218, 192, 176, 160, 145, 132, 120, 105, 91, 43 (base peak).

Crystal data for $C_{15}H_{19}NO_4$: Single crystals of **3d** suitable for X-ray crystallography were grown from *n*-hexane–EtOAc. *M* = 277.32, monoclinic, space group *P*21/*c*, *a* = 18.198(6), *b* = 5.149(2), *c* = 15.990(5) Å, *β* = 99.83(6)°, *λ* = 0.71073, *V* = 1476.6(8) $Å^3$, *z* = 4, D_{calc} = 1.247 mg/M^3, *μ* = 0.09 mm^{-1}, *T* = 293(2) K, refinement for data with I > 2σ(I) (1640 reflections, R_{int} = 0.0539) gave *R*1(*F*) = 0.0617 and w*R*2(F^2) = 0.1498 for all data.

Methyl 3-Acetamido-3-(4-acetoxyphenyl)-2-acetylpropanoate (4e)[4c]
Yield (after chromatography): 61% (soln), 53% (solvent-free).

***pref*-Isomer**
White crystals [EtOAc–petroleum ether (bp 60–80 °C)]; mp 170 °C.

IR (KBr): 3320, 1760, 1710, 1640, 1430, 1360, 1110, 1040, 910, 860, 840, 815, 670 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.00 (s, 3 H), 2.17 (s, 3 H), 2.28 (s, 3 H), 3.71 (s, 3 H), 4.05–4.07 (d, *J* = 5.6 Hz, 1 H), 5.72–5.77 (m, 1 H), 6.90–6.94 (d, *J* = 8.9 Hz, 1 H), 7.03–7.06 (d, *J* = 8.6 Hz, 2 H), 7.28–7.31 (d, *J* = 8.6 Hz, 2 H).

Methyl 3-Acetamido-2-acetyl-3-(4-bromophenyl)propanoate (4f)[4c]
Yield (after chromatography): 87% (soln), 81% (solvent-free).

***pref*-Isomer**
White crystals [EtOAc–petroleum ether (bp 60–80 °C)]; mp 146 °C.

IR (KBr): 3320, 1740, 1710, 1645, 1540, 1430, 1370, 1280, 1220, 1160, 1040, 1010, 845 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.01 (s, 3 H), 2.16 (s, 3 H), 3.73 (s, 3 H), 4.05–4.06 (d, *J* = 5.4 Hz, 1 H), 5.66–5.71 (m, 1 H), 6.92–6.95 (d, *J* = 8.9 Hz, 1 H), 7.15–7.18 (d, *J* = 8.2 Hz, 2 H), 7.43–7.46 (d, *J* = 8.2 Hz, 2 H).

Methyl 3-Acetamido-2-acetyl-3-(4-fluorophenyl)propanoate (4g)[4c]
Yield (after chromatography): 87% (soln), 84% (solvent-free).

***pref*-Isomer**
White crystals [EtOAc–petroleum ether (bp 60–80 °C)]; mp 116 °C.

IR (KBr): 3320, 1740, 1710, 1650, 1530, 1510, 1435, 1370, 1230, 1160, 1110, 1040, 845 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.01 (s, 3 H), 2.16 (s, 3 H), 3.71 (s, 3 H), 4.05–4.07 (d, *J* = 5.6 Hz, 1 H), 5.69–5.74 (m, 1 H), 6.91–6.94 (d, *J* = 8.4 Hz, 1 H), 6.98–7.03 (t, *J* = 8.6 Hz, 2 H), 7.24–7.29 (t, *J* = 6.8 Hz, 2 H).

Methyl 3-Acetamido-2-acetyl-3-(4-cyanophenyl)propanoate (4h)[4c]
Yield (after chromatography): 75% (soln), 65% (solvent-free).

***pref*-Isomer**
White crystals [EtOAc–petroleum ether (bp 60–80 °C)]; mp 140 °C.

IR (KBr): 3325, 2230, 1716, 1655, 1537, 1366, 1230, 1040, 851, 596, 567 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.07 (s, 3 H), 2.16 (s, 3 H), 3.75 (s, 3 H), 4.09–4.11 (d, *J* = 5.0 Hz, 1 H), 5.73–5.78 (m, 1 H), 7.01–7.04 (d, *J* = 8.7 Hz, 1 H), 7.40–7.43 (d, *J* = 8.7 Hz, 2 H), 7.61–7.64 (d, *J* = 8.2 Hz, 2 H).

***N*-[2-Acetyl-3-oxo-1-phenylbutyl]acetamide (5a)**
White crystals [EtOAc–petroleum ether (bp 60–80 °C)]; yield (after chromatography): 91% (soln), 91% (solvent-free); mp 132–133 °C.

IR (KBr): 3360, 2970, 1700, 1650, 1530, 1455, 1360, 1300, 1270, 1200, 1160, 1105, 955, 890, 760, 710, 620 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.01 (s, 3 H), 2.09 (s, 3 H), 2.27 (s, 3 H), 4.30–4.32 (d, *J* = 5.6 Hz, 1 H), 5.82–5.87 (m, 1 H), 7.10–7.13 (d, *J* = 7.9 Hz, 1 H), 7.25–7.35 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$, proton decoupled): δ = 23.2, 29.9, 31.0, 51.9, 70.4, 126.3, 127.8, 128.8, 139.2, 169.7, 202.6, 205.2.

MS (TOF): *m*/*z* = 270.01 [M^+ + Na].

Anal. Calcd for $C_{14}H_{17}O_3N$: C, 67.99; H, 6.92; N, 5.66. Found: C, 67.91; H, 7.01; N, 5.19.

***N*-[2-Acetyl-1-(4-nitrophenyl)-3-oxobutyl]acetamide (5b)[4b]**
Light yellow crystals [EtOAc–petroleum ether (bp 60–80 °C)]; yield (after chromatography): 57% (soln), 53% (solvent-free); mp 179 °C.

IR (KBr): 3260, 1720, 1700, 1660, 1610, 1595, 1415, 1370, 1355, 1290, 1250, 1150, 1100, 980, 855, 780, 750, 700, 600 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.05 (s, 3 H), 2.10 (s, 3 H), 2.35 (s, 3 H), 4.32–4.33 (d, *J* = 4.9 Hz, 1 H), 5.89–5.94 (m, 1 H), 7.09–7.12 (d, *J* = 9.0 Hz, 1 H), 7.46–7.49 (d, *J* = 8.6 Hz, 2 H), 8.21–8.23 (d, *J* = 6.4 Hz, 2 H).

***N*-[2-Acetyl-1-(4-chlorophenyl)-3-oxobutyl]acetamide (5c)**
White crystals [EtOAc–petroleum ether (bp 60–80 °C)]; yield (after chromatography): 90% (soln), 89% (solvent-free); mp 168 °C.

IR (KBr): 3290, 2910, 1715, 1695, 1640, 1530, 1490, 1400, 1370, 1360, 1305, 1285, 1245, 1190, 1170, 1150, 1090, 1010, 970, 830, 800, 745, 715, 685, 620, 600 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.99 (s, 3 H), 2.05 (s, 3 H), 2.27 (s, 3 H), 4.23–4.25 (d, *J* = 5.5 Hz, 1 H), 5.77–5.82 (m, 1 H), 7.00–7.03 (d, *J* = 9.0 Hz, 1 H), 7.19–7.22 (d, *J* = 8.5 Hz, 2 H), 7.27–7.30 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$, proton-decoupled): δ = 23.2, 29.9, 31.1, 51.3, 70.3, 127.9, 128.9, 133.6, 137.8, 169.9, 202.2, 204.9.

MS (ES): *m*/*z* = 304.05 [M^+ + Na], 306.07 [M^+ + Na + 2].

Anal. Calcd for $C_{14}H_{16}ClO_3N$: C, 59.68; H, 5.72; N, 4.97. Found: C, 59.63; H, 5.94; N, 4.72.

***N*-[2-Acetyl-1-(4-methylphenyl)-3-oxobutyl]acetamide (5d)[4a]**
White crystals [EtOAc–petroleum ether (bp 60–80 °C)]; yield (after chromatography: 70% (soln), 68% (solvent-free); mp 151 °C.

IR (KBr): 3290, 1715, 1690, 1635, 1540, 1370, 1355, 1305, 1290, 1245, 1145, 1085, 965, 810, 740 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.98 (s, 3 H), 2.09 (s, 3 H), 2.25 (s, 3 H), 2.30 (s, 3 H), 4.26–4.28 (d, *J* = 5.9 Hz, 1 H), 5.79–5.84 (m, 1 H), 6.90–6.93 (d, *J* = 8.9 Hz, 1 H), 7.10–7.16 (m, 4 H).

***N*-[1-(4-Acetoxyphenyl)-2-acetyl-3-oxobutyl]acetamide (5e)[4b]**
White crystals [EtOAc–petroleum ether (bp 60–80 °C)]; yield (after chromatography): 89% (soln), 85% (solvent-free); mp 145 °C.

IR (KBr): 3600, 3280, 1755, 1730, 1700, 1650, 1550, 1370, 1200, 1170, 1140, 1110, 960, 910, 880, 850, 660, 620 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.99 (s, 3 H), 2.10 (s, 3 H), 2.29 (s, 6 H), 4.25–4.27 (d, *J* = 5.6 Hz, 1 H), 5.82–5.87 (m, 1 H), 7.00–7.07 (m, 3 H), 7.27–7.29 (d, *J* = 8.7 Hz, 2 H).

***N*-[2-Acetyl-1-(4-cyanophenyl)-3-oxobutyl]acetamide (5h)**
White crystals [EtOAc–petroleum ether (bp 60–80 °C)]; yield (after chromatography): 92% (soln), 90% (solvent-free); mp 165 °C.

IR (KBr): 3265, 3000, 2960, 2240, 1720, 1700, 1660, 1610, 1550–1470, 1420, 1370, 1420, 1370, 1360, 1310, 1290, 1250, 1210, 1170, 1155, 1100, 1080, 975, 890, 830, 770, 625, 600 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.03 (s, 3 H), 2.09 (s, 3 H), 2.33 (s, 3 H), 4.28–4.29 (d, *J* = 4.9 Hz, 1 H), 5.84–5.89 (m, 1 H), 7.06–7.09 (d, *J* = 8.9 Hz, 1 H), 7.39–7.42 (d, *J* = 8.1 Hz, 2 H), 7.62–7.65 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$, proton-decoupled): δ = 23.2, 29.8, 31.3, 51.3, 69.4, 111.7, 118.3, 127.2, 132.6, 144.7, 169.9, 201.9, 204.8.

MS (TOF): *m*/*z* = 295.10 [M^+ + Na].

Anal. Calcd for $C_{15}H_{16}O_3N_2$: C, 66.16; H, 5.92; N, 10.28. Found: C, 65.99; H, 5.94; N, 10.04.

***N*-[2-Acetyl-1-(4-methoxyphenyl)-3-oxobutyl]acetamide (5i)[4b]**
White crystals [EtOAc–petroleum ether (bp 60–80 °C)]; yield (after chromatography): 61% (soln), 62% (solvent-free); mp 150 °C.

IR (KBr): 3300, 3060, 2960, 2840, 1720, 1700, 1650, 1585, 1530, 1510, 1360, 1305, 1290, 1250, 1180, 1150, 1090, 1030, 970, 830, 735, 600 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.98 (s, 3 H), 2.10 (s, 3 H), 2.23 (s, 3 H), 3.77 (s, 3 H), 4.24–4.26 (d, *J* = 6.1 Hz, 1 H), 5.76–5.81 (m, 1 H), 6.82–6.85 (d, *J* = 8.7 Hz, 2 H), 6.88–6.91 (d, *J* = 9.3 Hz, 1 H), 7.16–7.19 (d, *J* = 8.7 Hz, 2 H).

***N*-[1-(1-Acetyl-2-oxopropyl)octyl]acetamide (5j)**
White crystals [EtOAc–petroleum ether (bp 60–80 °C)]; yield (after chromatography): 85% (soln), 92% (solvent-free); mp 118 °C.

IR (KBr): 3287, 2920, 2856, 1716, 1699, 1651, 1553, 1361, 1284, 1149, 1138 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.85–0.89 (t, *J* = 6.5 Hz, 3 H), 1.25–1.67 (m, 12 H), 1.93 (s, 3 H), 2.17 (s, 3 H), 2.29 (s, 3 H), 3.89–3.91 (d, *J* = 4.0 Hz, 1 H), 4.60–4.67 (m, 1 H), 6.38–6.41 (d, *J* = 9.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$, proton-decoupled): δ = 14.0, 22.5, 23.2, 26.5, 29.1, 29.2, 29.8, 31.3, 31.7, 33.8, 48.6, 68.5, 169.9, 204.0, 205.8.

MS (TOF): *m*/*z* = 292.18 [M^+ + Na].

Anal. Calcd for $C_{15}H_{27}NO_3$: C, 66.88; H, 10.10; N, 5.19. Found: C, 67.08; H, 10.08; N, 4.83.

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(7) Crystallographic data of the compound *pref*-**16** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 601470. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].