One-Portion Synthesis of 2-Acetoxy Carbonyl Compounds from Aldehydes by Using an Acetylated Masked Acyl Cyanide

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Abstract: α-Acetoxy esters or amides were synthesized directly and in one portion from aldehydes and alcohols or amines by one-carbon homologation using a masked acyl cyanide reagent bearing an acetyl group.

Key words: masked acyl cyanide, one-portion synthesis, 2-acetoxy esters, 2-acetoxy amides, umpolung

Reagents of the general types 1, 2, 4 and 3 can be classified as one-carbon-homologated acyl anion equivalents (Scheme 1). Substituents Y1–Y6 stabilize the anion of the central carbon, and can be hydroxy-group equivalents, which lead to carboxylic acids 7, mainly through hydrolysis. Steps I and II have been successfully demonstrated with various forms of reagents 1–3; the first of these steps corresponds to the formation of a carbanion and the subsequent C–C bond-formation reaction, whereas the second step represents the unmasking of the elaborate form to give a carbonyl compound. If further transformation to afford an ester 9 or amide 10 is required, the unmasked carbonyl compound 7 can be condensed with an alcohol or an amine, respectively (step III). In some cases, an activated carbonyl compound 8 can be generated from derivatives 4–6 without the need for any additional condensation reagent, such as a carbodiimide.

Accordingly, reactions involving acyl-anion equivalents have always involved the transformation of reagents 1–3 in several steps. It is advisable to carry out Steps I and III under aprotic neutral-to-basic conditions, whereas protic and acidic conditions are often required for Step II. It would therefore appear to be impractical to mix all the essential chemicals in one portion; reagents for both hydrolysis and dehydration reactions would need to be added together, and the appropriate pH values could not be achieved. Even methods involving successive addition of the reagents to a single vessel (i.e., a one-pot reaction) may be impractical because delicate control would be required with regard to the interval between each addition and the number of equivalents of each reagent added. In fact, no one-pot or one-portion reaction (in which all the substrates are added at once) had ever been successfully demonstrated for reagents 1–3 until, by using masked acyl cyanide (MAC) reagents,1 represented as H–MAC–X–R0 or H–MAC–R0 (R0 = Ac, TBS, TIPS), we succeeded in achieving such a reaction.8–13

Previously Reported One-Portion Reactions Using MAC Reagents: In our earlier publications,14–22 as well as in some recent papers,24,25 we reported conventional multistep reactions. The first one-portion reaction8 was demonstrated by using H–MAC–TBS (15; Scheme 2).23 The three components – an aldehyde or a ketone (11), an amine (13), and H–MAC–TBS – were mixed in one portion to afford α-siloxy amides 17a in excellent yields (Scheme 2).8 The synthesis of α-siloxy esters 17b was also demonstrated.9,10 The first one-portion reaction using H–MAC–Ac (16)23 was the synthesis of N-methyl-N-acetyl-α-amino acid methyl esters of type 17c.12 Weinreb amide derivatives, which are broadly classified as 17a, were also successfully prepared.13

The proposed intermediate A2 is the key to the one-portion reaction. After the C–C bond formation (A1), the R group migrates from the oxygen of the MAC reagent to the anionic X atom (A2). The intramolecular migration of R triggers the elimination of a cyanide anion to generate the activated carbonyl intermediate, the acyl cyanide 18, which can be transformed into 17 without the use of a con-
densation reagent such as a carbodiimide. On the basis of this mechanism, we can identify two factors that are essential for the one-portion reaction; the first is the use of a MAC reagent with a migratory R<sup>0</sup> group, and the second is the presence of an electrophile, E<sup>+</sup>, that generates an intramolecular anionic X atom in a position neighboring R<sup>0</sup>. Conversely, if a multistep reaction rather than a one-portion reaction is required, we can choose either acetal-type protecting groups for R<sup>0</sup> or an electrophile that does not possess a C=X functional group.

The difference between the conventional reagents 1–3 and MAC reagents may be explained as follows. In the case of 1–3, the unmasking step from 4–6 to 7 or 8 is initiated by cleavage of the bond between the central carbon and one of the Y<sup>n</sup> groups, as shown in Scheme 3. For the bond-cleavage reaction, water or its chemical equivalent must directly attack the central carbon atom of 4–6 to produce the C=O functionality. The unmasking step for MAC reagents, in contrast, is initiated by bond cleavage between R<sup>0</sup> and oxygen (19) (Scheme 3). In the one-portion reaction, additional reagents for hydrolysis are not necessary because the neighboring anionic oxygen or nitrogen atom can intramolecularly cleave the O–R<sup>0</sup> bond. From this point of view, the molecular design of MAC reagents is significantly different from that of conventional reagents.

**Comparison with the Ugi and Passerini Reactions**: The Ugi and Passerini reactions<sup>27</sup> are convenient and useful methods for the preparation of esters 17<sup>f</sup> and 17<sup>h</sup>, provided that either R<sup>4</sup> or R<sup>5</sup> is a hydrogen atom (Scheme 4). In contrast, MAC reagents can potentially afford not only 17<sup>f</sup> and 17<sup>h</sup>, but also the α-siloxy products 17<sup>a</sup>–d, esters 17<sup>b</sup>, 17<sup>c</sup>, 17<sup>e</sup>, and 17<sup>g</sup>, and tertiary amides of the entire series of 17 compounds. Accordingly, MAC reagents have the potential to be key molecules for efficient multicomponent reactions (MCR), and combinatorial syntheses.

The key reagent in Ugi and Passerini reactions is isocyanide, which is not classified as any of reagents 1–3. The isocyanide, derived from primary amine R<sup>7</sup>NH<sub>2</sub>, must be freshly prepared each time the Passerini reaction is carried out. In contrast, when using MAC reagents, both primary and secondary amines 13 can be used without any pretreatment in the one-portion reaction. Therefore, our methodology can potentially be applied to the synthesis of compounds 17 bearing amines with unstable structures. In addition, the key reagent (the MAC reagent) can be stored for several months, and H–MAC–Ac is commercially available<sup>28</sup>.

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**Scheme 2**  One-portion reaction using MAC reagents and the proposed mechanism

**Scheme 3**  Initiation of unmasking step: differences in bond cleavage

**Scheme 4**  Ugi reaction and Passerini reaction
An unavoidable disadvantage of MAC reagents is the generation of hydrogen cyanide, a dangerous gas, during the reaction. Recovery and recycling of the cyanide anion should be considered, particularly in the case of industrial-scale reactions; fortunately, safe methods have been established for the treatment of cyanide sources on an industrial scale.

As the original developers of MAC reagents, we wished to examine all possible one-portion reactions using these reagents; the only compounds remaining to be examined (17c, d, f–h) are the focus of this work.

First, we summarize various unsuccessful attempts to prepare representative compounds of types 17c and 17d. It is likely that the low affinity between Si and N prevented the intramolecular migration process, as shown in Scheme 5. Fortunately, our alternative two- or three-step strategies are applicable if α-amino amide derivatives or α-amino ester derivatives are the target molecules.

Scheme 5  Unsuccessful preparation of representative compound of types 17c or 17d

Next, we examined the one-portion reaction using aromatic aldehydes 20 with H–MAC–Ac (16) and methanol to afford 21, which are α-acetoxy esters of type 17g (Table 1). As shown in entries 1–7, 21a was obtained from 4-methylbenzaldehyde (20a) in good-to-excellent yields in the presence of various tertiary amines. In contrast, the use of an inorganic base did not bring about the desired reaction (entry 8). Since imidazole (entry 1) gave the largest yield and highest purity (cf. entries 2–8), we used these conditions when examining the one-portion reactions of aromatic aldehydes (entries 9–12). In all cases, the products (21b–e) were obtained in excellent yields. The differences in electronegativity of the substituted aromatic rings did not have a significant influence on the desired one-portion reactions.

In contrast to aromatic aldehydes, a representative aliphatic aldehyde, 2-ethylbutanal (22a), was transformed into methyl 2-acetoxy-3-ethylpentanoate (23a) in moderate yield when methanol was used as the solvent (Scheme 6). The main byproduct was the cyanohydrin, which was efficiently inhibited in ether at lower temperatures (3.0 equivalents versus aldehyde) were examined in ether at –20 °C (Table 2). As expected, the yield of 23a was improved (entry 1). By comparing the results shown in entries 2–4, we found that imidazole (entry 1) was the most effective base. Thus, the conditions used for entry 1 were applied to other aliphatic aldehydes (entries 5–8), and the desired products 23b–d were obtained in good yields. Although an unexpectedly large amount of cyanohydrin was obtained as a byproduct when 22c was used (entry 6), the yield of 23e was improved when three equivalents of 16 were used (entry 7).

Next, we examined one-portion reactions using 4-methylbenzaldehyde to afford α-acetoxylated amides 24 as a representative example of compounds of type 17h. As shown in Tables 3, 4-methylbenzaldehyde was efficiently transformed into 24. Even in the presence of water, the one-portion reaction proceeded in excellent yield (entry 2).

### Table 1  One-Portion Reaction Using Aromatic Aldehydes with 16 in Methanol

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde 20</th>
<th>Base</th>
<th>Yield (%) of 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-MeC₆H₄CHO (20a)</td>
<td>imidazole</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>pyridine</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>DMAP</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Et₃N</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>iPr₂NEt</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>4-PPY⁺</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>NMMᵃ</td>
<td>72</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>K₂CO₃</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>4-MeOC₆H₄CHO (20b)</td>
<td>imidazole</td>
<td>81</td>
</tr>
<tr>
<td>10</td>
<td>PhCHO (20c)</td>
<td>imidazole</td>
<td>84</td>
</tr>
<tr>
<td>11</td>
<td>4-O₂NC₆H₄CHO (20d)</td>
<td>imidazole</td>
<td>91</td>
</tr>
<tr>
<td>12</td>
<td>4-NCC₆H₄CHO (20e)</td>
<td>imidazole</td>
<td>84</td>
</tr>
</tbody>
</table>

ᵃ 4-PPY = 4-(pyrrolidin-1-yl)pyridine.
ᵇ N-Methylmorpholine.

Scheme 6  First attempt at one-portion reaction with 16 using an aliphatic aldehyde
Weakly basic amines, such as aniline, gave 24c in the presence of 4-(dimethylamino)pyridine (entry 4 versus entry 3). The tertiary amides 24d and 24e, which cannot be prepared by the Passerini reaction, were synthesized with H–MAC–Ac (entries 5 and 6).

Finally, one-portion reactions to afford 17h using aliphatic aldehydes were examined (Scheme 7). When 2-ethylbutanal (22a), butylamine, and H–MAC–Ac were mixed in one portion under the standard conditions used for the reaction in Table 3, the desired product 25 was not detectable at all, and N-butylacetamide was the sole product. When the conditions used to obtain esters 23 from aliphatic aldehydes were applied, 25 was obtained in 23% yield along with 39% of N-butylacetamide. In the case of cyclohexanecarboxaldehyde, the desired product 26 was obtained in 48% yield, along with 22% of N-butylacetamide.

Table 2  One-Portion Reaction Using Aliphatic Aldehydes with 16 and Methanol in Diethyl Ether

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde 22</th>
<th>Base</th>
<th>Yield (%) of 23</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₂CHCHO (22a)</td>
<td>imidazole</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>pyridine</td>
<td></td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>DMAP</td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>Et₃N</td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>Me₂CHCHO (22b)</td>
<td>imidazole</td>
<td>69</td>
</tr>
<tr>
<td>6</td>
<td>Me(CH₂)₇CH₂CHO (22c)</td>
<td>imidazole</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>imidazole</td>
<td></td>
<td>57a</td>
</tr>
<tr>
<td>8</td>
<td>PhCH₂CH₂CHO (22d)</td>
<td>imidazole</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>BuCH(Et)CH(O)CHO (22e)</td>
<td>imidazole</td>
<td>81</td>
</tr>
</tbody>
</table>

a 3.0 equiv of 16 were used.

Table 3  One-Portion Reaction Using 4-Methylbenzaldehyde with 16 and Various Amines

<table>
<thead>
<tr>
<th>Entry</th>
<th>R'R₄NH</th>
<th>Time (min)</th>
<th>Yield (%) of 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BuNH₂</td>
<td>15</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>NH₃a</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>PhNH₂</td>
<td>120</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>PhNH₂ + DMAP (0.10 equiv)</td>
<td>120</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>Et₂NH</td>
<td>15</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>morpholine</td>
<td>120</td>
<td>86</td>
</tr>
</tbody>
</table>

a 10% aqueous solution (3.0 equiv).

The proposed mechanism for the production of N-butylacetamide is shown in Scheme 8. In the case of 4-methylbenzaldehyde, the rate of nucleophilic addition by 16 (k₁) may be much greater than the rate of nucleophilic attack by butylamine on the acetyl group of the MAC reagent (k₄). However, rates k₃ and k₄ seem to be very similar, resulting in a mixture of N-butylacetamide and either 25 or 26.

A final attempt at a one-portion reaction to afford 28, as a representative example of a compound of type 17f, led us to conclude that we could not achieve a reproducible re-
sult for the reaction using 27, even by changing the conditions (Scheme 9). The major detectable and isolable compound in a mixture of unidentified products was N-butylacetamide, which was obtained in various yields. Since imines are less reactive than the corresponding aldehydes towards ordinary nucleophiles, $k_2$ is rather smaller than $k_4$, even if an aromatic substituent is present at the C=N bond.

To summarize, we describe the results of the one-portion reactions using H–MAC–Ac (16), and demonstrate the current scope and limitations of the process. A summary of the results obtained in this work, along with those obtained for one-portion MAC reactions in several previous studies, is shown in Scheme 10. We are currently examining the possibility of further optimization to solve the problems currently associated with these reactions, and hope that the one-portion reaction will have a wide applicability.

**Caution!** Two equivalents of hydrogen cyanide gas are generated in the one-portion reactions; carry out all reactions under an efficient hood.

$^1$H NMR spectra were recorded in CDCl$_3$ or CD$_3$OD solution and referenced to TMS (0.00 ppm) using 400- or 300-MHz spectrophotometers (Jeol AL400 and Jeol AL300, respectively). $^{13}$C NMR spectra were measured in CDCl$_3$ or CD$_3$OD solution and referenced to CDCl$_3$ (77.0 ppm) or CD$_3$OD (49.0 ppm) using 100- or 75-MHz spectrophotometers (Jeol AL400 and Jeol AL300, respectively). Chemical shifts are reported in ppm. IR spectra were recorded on a FT-IR spectrometer (Jasco FT-IR 420). Mass spectra were obtained on an EI or an ESI mass spectrometer (Jeol JMS-DX303 and Waters Micromass LCT Premier, respectively). Column chromatography was performed on silica gel. Thin-layer chromatography was performed on precoated plates (0.25 mm, silica gel). All reactions were performed in oven-dried glassware under a positive pressure of argon, unless otherwise noted. Reaction mixtures were stirred magnetically. CH$_2$Cl$_2$ and MeCN were distilled over P$_2$O$_5$. MeOH was distilled over Mg. DCE was distilled over CaH$_2$. Et$_2$O was distilled over LiAlH$_4$. Anhydrous THF was purchased from Kanto Chemical Co., Inc.

**α-Acetoxyacetic Acid Methyl Esters; General Procedures**

**Method A (21a–e)**
H–MAC–Ac (16: 29.8 mg, 0.24 mmol, 1.2 equiv) was added to a solution of 20 (0.20 mmol, 1.0 equiv) and base (0.30 mmol, 1.5 equiv) in anhyd MeOH (5 mL) at r.t., and the mixture was stirred for 3 h at r.t. The resulting solution was concentrated in vacuo, and the residue was purified by column chromatography and, optionally, crystallization.

**Method B (23a–e)**
H–MAC–Ac (16: 49.6 mg, 0.40 mmol, 1.2 equiv) was added to a solution of 22 (0.33 mmol, 1.0 equiv), imidazole (34.0 mg, 0.50 mmol, 1.5 equiv), and MeOH (41 μL, 1.0 mmol, 3.0 equiv) in anhyd Et$_2$O (5 mL) at –20 °C, and the mixture was stirred at –20 °C. The resulting mixture was concentrated in vacuo, and the residue was purified by column chromatography and, optionally, crystallization.

**Methyl Acetoxy(4-methylphenyl)acetate (21a)**

Purified by column chromatography [silica gel, hexane–EtOAc (9:1)] and crystallization (Et$_2$O/hexane) as colorless crystals; yield: 41.3 mg (0.186 mmol, 93%); mp 69–70 °C.
1H NMR (400 MHz, CDCl3): δ = 7.35 (d, J = 8.0 Hz, 2 H, aromatic), 7.20 (d, J = 8.0 Hz, 2 H, aromatic), 5.90 (s, 1 H, OCH), 3.71 (s, 3 H, OCH3), 2.36 (s, 3 H, ArCH3), 2.18 [s, 3 H, C(O)CH3].

13C NMR (100 MHz, CDCl3): δ = 170.2 (C=O), 169.2 (C=O), 139.1 (C), 130.6 (C), 129.5 (CH × 2), 127.5 (CH × 2), 74.2 (CH), 52.5 (CH3), 21.2 (CH3), 20.7 (CH3).


Methyl Acetoxy(phenyl)acetate (21c)29,32,33

Methyl Acetoxy(4-methoxyphenyl)acetate (21b)31

1H NMR (400 MHz, CDCl3): δ = 7.48–7.45 (m, 2 H, aromatic), 7.22–7.17 (m, 3 H, aromatic), 5.01 (t, J = 6.4 Hz, 1 H, OCH), 3.73 (s, 3 H, OCH3), 2.13 [s, 3 H, C(O)CH3], 1.84–1.78 (m, 2 H, aliphatic), 1.43–1.20 (m, 14 H, aliphatic), 0.87 (t, J = 7.2 Hz, 3 H, CHCH3).

13C NMR (100 MHz, CDCl3): δ = 170.1 (C=O), 169.2 (C=O), 139.0 (CH), 129.0 (CH), 128.6 (CH), 52.5 (CH3), 20.7 (CH3).


Methyl 2-Acetoxy-3-ethylpentanoate (23a)34–37

Methyl 2-Acetoxy-4-phenylbutanoate (23d)43

1H NMR (400 MHz, CDCl3): δ = 4.97 (t, J = 4.4 Hz, 1 H, OCH), 3.73 (s, 3 H, OCH3), 2.13 [s, 3 H, C(O)CH3], 1.84–1.78 (m, 2 H, aliphatic), 1.43–1.20 (m, 14 H, aliphatic), 0.87 (t, J = 6.4 Hz, 3 H, CH3).

13C NMR (100 MHz, CDCl3): δ = 170.8 (C=O), 170.5 (C=O), 72.3 (CH2), 52.2 (CH2), 31.9 (CH3), 31.1 (CH), 29.5 (CH2), 29.4 (CH3), 29.3 (CH3), 29.2 (CH2), 25.1 (CH3), 22.7 (CH2), 20.7 (CH3), 14.2 (CH3).


Methyl 2-Acetoxyundecanoate (23c)

Purified as a colorless oil by column chromatography [silica gel, hexane–EtOAc (9:1)]; yield: 48.6 mg (0.188 mmol, 57%).

FT-IR (KBr): 3111, 3082, 2958, 2360, 1714, 1525, 1350, 860 cm–1.

1H NMR (400 MHz, CDCl3): δ = 4.97 (t, J = 4.4 Hz, 1 H, OCH), 3.73 (s, 3 H, OCH3), 2.13 [s, 3 H, C(O)CH3], 1.84–1.78 (m, 2 H, aliphatic), 1.43–1.20 (m, 14 H, aliphatic), 0.87 (t, J = 6.4 Hz, 3 H, CH3).

13C NMR (100 MHz, CDCl3): δ = 170.8 (C=O), 170.5 (C=O), 72.3 (CH2), 52.2 (CH2), 31.9 (CH3), 31.1 (CH), 29.5 (CH2), 29.4 (CH3), 29.3 (CH3), 29.2 (CH2), 25.1 (CH3), 22.7 (CH2), 20.7 (CH3), 14.2 (CH3).


Methyl 2-Acetoxy-4-phenylbutanoate (23d)43

Methyl Acetoxy(4-methoxyphenyl)acetate (21b)31

Purified as a colorless oil by column chromatography [silica gel, hexane–EtOAc (9:1)]; yield: 36.9 mg (0.228 mmol, 69%).

FT-IR (KBr): 3111, 3082, 2958, 2360, 1714, 1525, 1350, 860 cm–1.

1H NMR (400 MHz, CDCl3): δ = 4.84 (d, J = 4.4 Hz, 1 H, OCH), 3.75 (s, 3 H, OCH3), 2.30–2.14 (m, 1 H, CH(CH3)2), 2.15 [s, 3 H, C(O)CH3], 1.01 (d, J = 7.2 Hz, 3 H, CHCH3).

13C NMR (100 MHz, CDCl3): δ = 170.6 (C=O), 170.5 (C=O), 73.6 (CH2), 52.0 (CH3), 43.1 (CH), 22.6 (CH2), 22.3 (CH), 20.6 (CH), 11.6 (CH), 11.5 (CH).


Methyl 2-Acetoxyundecanoate (23c)

Purified as a colorless oil by column chromatography [silica gel, hexane–EtOAc (9:1)]; yield: 61.64 mg (0.248 mmol, 75%).

1H NMR (400 MHz, CDCl3): δ = 5.11 (d, J = 3.6 Hz, 1 H, OCH), 3.74 (s, 3 H, OCH3), 2.14 [s, 3 H, C(O)CH3], 1.81–1.74 (m, 1 H, CH(CH3)2), 1.49–1.28 (m, 4 H, CHCH3CH2CH2), 0.90 (t, J = 6.8 Hz, 3 H, CHCH3CH2).

13C NMR (100 MHz, CDCl3): δ = 170.5 (C=O), 170.5 (C=O), 73.6 (CH2), 52.0 (CH3), 43.1 (CH), 22.6 (CH2), 22.3 (CH), 20.6 (CH), 11.6 (CH), 11.5 (CH).

C NMR (100 MHz, CDCl3): δ = 170.3 (C=O), 170.1 (C=O), 140.1 (C), 128.3 (CH×2), 128.2 (CH×2), 126.0 (CH), 71.4 (CH), 52.1 (CH2), 32.5 (CH2), 31.2 (CH2), 20.5 (CH3).


2-(Phenylamino)-1-(4-methylphenyl)-2-oxoethyl Acetate (24c)

Purified by column chromatography [silica gel, hexane–EtOAc (4:1)] and crystallized as colorless crystals (Et2O/hexane); yield: 61.5 mg (0.267 mmol, 81%); 1:1 mixture of diastereomers.

FT-IR (KBr): 2958, 2873, 2306, 1739, 1600, 1539, 1043, 985, 752, 735, 492 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 7.77 (br s, 1 H, NH), 7.52 (d, J = 8.0 Hz, 2 H, aromatic), 7.38 (d, J = 8.0 Hz, 2 H, aromatic), 7.31 (t, J = 8.0 Hz, 2 H, aromatic), 7.20 (d, J = 8.0 Hz, 2 H, aromatic), 7.12 (t, J = 8.0 Hz, 1 H, aromatic), 6.16 (s, 1 H, OCH), 2.35 (s, 3 H, ArCH3), 2.23 [s, 3 H, C(O)CH3].

13C NMR (100 MHz, CDCl3): δ = 169.0 (C=O), 166.3 (C=O), 139.2 (C), 138.6 (C), 132.1 (CH×2), 129.5 (CH×2), 129.0 (CH×2), 127.4 (CH×2), 124.8 (C), 121.0 (CH), 75.6 (CH), 21.3 (CH3), 21.2 (CH3).


2-(Butylamino)-1-(4-methylphenyl)-2-oxoethyl Acetate (24a)

Purified as a colorless oil by column chromatography [silica gel, hexane–EtOAc (9:1)]; yield: 61.5 mg (0.267 mmol, 81%); 1:1 mixture of diastereomers.

FT-IR (neat): 2958, 2873, 2306, 1739, 1676, 1600, 1539, 1043, 978, 752, 735, 492 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 7.77 (br s, 1 H, NH), 7.52 (d, J = 8.0 Hz, 2 H, aromatic), 7.38 (d, J = 8.0 Hz, 2 H, aromatic), 7.31 (t, J = 8.0 Hz, 2 H, aromatic), 7.20 (d, J = 8.0 Hz, 2 H, aromatic), 7.12 (t, J = 8.0 Hz, 1 H, aromatic), 6.16 (s, 1 H, OCH), 2.35 (s, 3 H, ArCH3), 2.23 [s, 3 H, C(O)CH3].

13C NMR (100 MHz, CDCl3): δ = 169.0 (C=O), 166.3 (C=O), 139.2 (C), 138.6 (C), 132.1 (CH×2), 129.5 (CH×2), 129.0 (CH×2), 127.4 (CH×2), 124.8 (C), 121.0 (CH), 75.6 (CH), 21.3 (CH3), 21.2 (CH3).


2-(Diethylamino)-1-(4-methylphenyl)-2-oxoethyl Acetate (24d)

Purified by column chromatography [silica gel, hexane–EtOAc (4:1)] and crystallized as colorless crystals (Et2O/hexane); yield: 60.5 mg (0.230 mmol, 70%); mp 128–129 °C.

FT-IR (KBr): 2983, 1729, 1658, 1612, 1545, 1043, 818 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 7.34 (d, J = 8.0 Hz, 2 H, aromatic), 7.20 (d, J = 8.0 Hz, 2 H, aromatic), 6.14 (s, 1 H, OCH), 3.58–3.08 (m, 4 H, NCH2×2), 2.36 (s, 3 H, ArCH3), 2.15 [s, 3 H, C(O)CH3], 1.10 (t, J = 7.2 Hz, 3 H, NCH2CH3), 1.04 (t, J = 7.2 Hz, 3 H, NCH2CH3).

13C NMR (100 MHz, CDCl3): δ = 170.7 (C=O), 166.9 (C=O), 139.2 (C), 131.3 (C), 129.6 (CH×2), 128.5 (CH×2), 73.4 (CH), 41.4 (CH3), 40.6 (CH2), 21.3 (CH3), 21.0 (CH3), 13.6 (CH3), 12.8 (CH3).


1-(4-Methylphenyl)-2-(morpholin-4-yl)-2-oxoethyl Acetate (24e)

Purified as a colorless oil by column chromatography [silica gel, hexane–EtOAc (4:1)]; yield: 78.5 mg (0.283 mmol, 86% yield).

FT-IR (neat): 2966, 2921, 2858, 1741, 1662, 1439, 1236, 1158, 1028, 810 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 7.32 (d, J = 8.0 Hz, 2 H, aromatic), 7.21 (d, J = 8.0 Hz, 2 H, aromatic), 6.18 (s, 1 H, OCH), 3.78–3.12 (m, 8 H, NCH2CH2O–×2), 2.37 [s, 3 H, ArCH3], 2.16 [s, 3 H, C(O)CH3].

13C NMR (100 MHz, CDCl3): δ = 170.5 (C=O), 166.4 (C=O), 139.4 (C), 130.7 (C), 130.0 (CH×2), 128.1 (CH×2), 73.0 (CH), 66.6 (CH2), 66.0 (CH2), 45.7 (CH2), 42.5 (CH2), 21.2 (CH3), 20.8 (CH3).

1-(Butylamino)-3-ethyl-1-oxopentan-2-yl Acetate (25)

Purified as a colorless oil by column chromatography [silica gel, hexane–EtOAc (4:1)]; yield: 18.4 mg (0.0756 mmol, 23%); mp 73–74 °C.

Supporting Information

for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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References


(6) General structure 1 is from reference 3i.

(7) Although the term ‘masked acyl cyanide’ was mentioned in the following paper, generation of an ‘unmasked acyl cyanide’ was unsuccessful: Khatari, H. N.; Waldborsky, H. M. J. Org. Chem. 1978, 43, 734.


