Green synthesis of new acyl hydrazide derivatives by single and double aza-Michael reaction under solvent-free conditions

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ABSTRACT
In this paper, we describe a new, simple and efficient strategy for the formation of novel and valuable acyl hydrazide derivatives from reaction between diverse acyl hydrazides and \( \alpha, \beta \)-unsaturated esters in the presence of 1,4-diaza-bicyclo[2,2,2]octane (DABCO) – an inexpensive base – and tetrabutylammonium bromide (TBAB) – an ionic organic salt – under solvent-free conditions. In the reaction, double Michael adducts were produced in good yields in 7 h when acrylic esters were used as Michael acceptors. Surprisingly, no double Michael adducts were produced with fumaric esters, and single Michael adducts were the only products of these reactions in 10 h.

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Introduction

Hydrazides are important intermediates in organic synthesis (1), especially in the preparation of pharmaceuticals and agrochemicals. Their synthesis has attracted significant attention due to their utility as building blocks in many syntheses (2–4). Most of these compounds show interesting properties such as antituberculous agent (Isoniazid), HIV inhibitors, inhibitors of myeloperoxidase, glycogen phosphorylase, pesticides (5–7) and \( \beta \)-glucuronidase enzyme inhibitors (8). Also, these compounds have analgesic activity (9) and acyl hydrazides have been known as novel inhibitors of mammalian cathepsin B and cathepsin H (10).

The Michael reaction is one of the most important reactions in organic chemistry that, over the years, has drastically attracted the attention of researchers. This reaction has been considerably used in the formation of C-N, C-O, C-S and C-C bonds in modern organic synthesis (11–13). It is important to note that today, many scientists are interested in using diverse primary amines in the aza-Michael addition reaction to produce selectively mono- or bis-adduct by employing different catalysts and conditions (14–16). In this line, surprisingly, to the best of our knowledge, no emphasis has been put on the production of either the mono-adduct or the bis-adduct when using the acyl hyrazides as a primary amines, by aza-Michael addition reaction. With this background and in continuation of our interest in the aza-Michael addition of amides and imides to \( \alpha, \beta \)-unsaturated esters (17–20), herein we report for the first time, the synthesis of \( \beta \)-N-substituted derivatives of acyl hydrazides using Michael addition of these compounds to \( \alpha, \beta \)-unsaturated esters in solvent-free conditions (Scheme 1).

Experimental section

General

Acyl hydrazides and \( \alpha, \beta \)-unsaturated esters were synthesized in our laboratory according to the literature procedure (21, 22) and their structures were confirmed by IR spectroscopy and melting point. The progress of the reaction was followed by TLC using silica gel SILIG/UV
254 plates. 1H-NMR (400 MHz) and 13C NMR (100 MHz) spectra were recorded on a Bruker 400 MHz instrument. FT-IR spectra were recorded on a Perkin-Elmer RX-1 instrument. Mass spectra were recorded on a Shimadzu GC-MS-QP 1000PX. Elemental analysis for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. The melting points were determined in open capillaries with a Stuart Melting Point Apparatus and remained uncorrected. Chemical shifts were recorded in ppm downfield from tetramethylsilane. J values were given in Hz. Abbreviations used in 1H NMR are s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet).

General procedure for the Michael addition of acyl hydrazides to α,β-unsaturated esters

To a well ground mixture of acyl hydrazide (1.0 mmol), DABCO (1.0 mmol) and TBAB (1.0 mmol), α,β-unsaturated ester (2.5 mmol for acrylic ester and 1.2 mmol for fumaric ester) was added and mixed thoroughly with a glass rod. The resulting mixture was kept at room temperature (for acrylic esters) and in an oil bath at 70°C (for fumaric esters) for appropriate time (Table 3). The progress of reaction was monitored by TLC. After completion of reaction, the mixture was cooled to room temperature and dissolved in chloroform (20 mL). TBAB was recovered by the addition of water (15 mL × 3), then collected and dried under vacuum. The chloroform layer was washed with water (15 mL × 3). The organic layer was dried over anhydrous Na2SO4. The solvent was removed under reduced pressure and the resulting crude material was purified on short silica-gel column with ethyl acetate : n-hexane (1 : 9) as the eluent.

Physical and spectroscopic data of isolated products

Diethyl 3,3′-(2-benzoylhydrazine-1,1-diyl)dipropanoate (3a)

White crystal; mp 75–77°C; 1H NMR (CDCl3, 400 MHz): δ ppm 1.16 (t, 6H, J = 7.1 Hz, 2CH3), 2.60 (t, 4H, J = 6.5 Hz, 2CH2), 3.29 (t, 4H, J = 6.5 Hz, 2CH2N), 4.01 (q, 2H, J = 7.1 Hz, CH2O), 7.15–7.76 (m, 6H, 5CH-Ar, NH); 13C NMR (CDCl3, 100 MHz): δ ppm 13.0, 31.6, 51.5, 59.6, 125.9, 127.5, 130.8, 131.9, 165.6, 171.7; IR (KBr, cm⁻¹): 3223, 3059, 2985, 1733, 1651, 1182, 689. Anal. Calcd. for C17H24N2O5: C, 60.70; H, 7.19; N, 8.33. Found: C, 60.93; H, 7.34; N, 8.69.

Dibutyl 3,3′-(2-benzoylhydrazine-1,1-diyl)dipropanoate (3b)

White solid; mp 83–85°C [77–79°C (23)]; 1H NMR (CDCl3, 400 MHz): δ ppm 0.87 (t, 6H, J = 7.4 Hz, 2CH3), 1.29 (sextet, 4H, J = 7.4 Hz, 2CH2), 1.51 (quintet, 4H, J = 7.1 Hz, 2CH2), 2.59 (t, 4H, J = 6.7 Hz, 2CH2), 3.29 (t, 4H, J = 6.7 Hz, 2CH2N), 3.97 (t, 4H, J = 6.9 Hz, 2CH2O), 7.17 (s, 1H, NH), 7.24 (t, 2H, J = 7.4 Hz, 2CH-Ar), 7.50 (t, 1H, J = 7.3 Hz, CH-Ar), 7.74 (d, 2H, J = 7.1 Hz, 2CH-Ar); 13C NMR (CDCl3, 100 MHz): δ ppm 12.6, 18.0, 29.4, 31.7, 51.5, 63.5, 125.9, 127.5, 130.7, 132.0, 165.5, 171.7; IR (KBr, cm⁻¹): 3229, 3057, 2960, 1734, 1649, 1313, 1180, 680; MS: m/z 392 (M⁺, 6), 350 (13), 328 (47), 242 (100), 198 (44), 150 (43), 104 (16), 85 (19), 43 (46). Anal. Calcd. for C21H32N2O5: C, 64.26; H, 8.22; N, 7.14. Found: C, 64.58; H, 8.45; N, 7.02.

Dihexyl 3,3′-(2-benzoylhydrazine-1,1-diyl)dipropanoate (3c)

White solid; mp 52–55°C; 1H NMR (CDCl3, 400 MHz): δ ppm 0.86 (t, 6H, J = 6.8 Hz, 2CH3), 1.23–1.31 (m, 12H, 6CH2), 1.48–1.53 (m, 4H, 2CH2), 2.60 (t, 4H, J = 6.6 Hz, 2CH2), 3.28 (t, 4H, J = 6.6 Hz, 2CH2), 3.95 (t, 4H, J = 6.8 Hz, 2CH2N), 7.11 (s, 1H, NH), 7.24 (t, 2H, J = 7.2 Hz, 2CH-Ar), 7.51 (t, 1H, J = 7.4 Hz, CH-Ar), 7.75 (d, 2H, J = 7.2 Hz, 2CH-Ar); 13C NMR (CDCl3, 100 MHz): δ ppm 12.9, 21.4, 24.4, 27.3, 30.3, 31.6, 51.6, 63.9, 125.9, 127.5, 130.8, 131.8, 165.5, 171.8; IR (KBr, cm⁻¹): 3217, 3061, 2956, 1733, 1653, 1313, 1178, 697. Anal. Calcd. for C25H40N2O5: C, 64.26; H, 8.22; N, 7.14. Found: C, 64.58; H, 8.45; N, 7.02.

Diethyl 3,3′-(2-(4-nitrobenzoyl)hydrazine-1,1-diyl)dipropanoate (3d)

White crystal; mp 112–114°C; 1H NMR (CDCl3, 400 MHz): δ ppm 1.82 (t, 6H, J = 7.2 Hz, 2CH3), 2.61 (t, 4H, J = 6.0 Hz, CH2O), 7.15–7.76 (m, 6H, 5CH-Ar, NH); 13C NMR (CDCl3, 100 MHz): δ ppm 13.0, 31.6, 51.5, 59.6, 125.9, 127.5, 130.8, 131.9, 165.6, 171.7; IR (KBr, cm⁻¹): 3223, 3059, 2985, 1733, 1651, 1182, 689. Anal. Calcd. for C17H24N2O5: C, 60.70; H, 7.19; N, 8.33. Found: C, 60.93; H, 7.34; N, 8.69.
2CH3), 3.29 (m, 2H, CH2N), 4.04 (q, 4H, J = 7.0 Hz, 2OCH2), 7.57 (sbr, 1H, NH), 7.95 (d, 2H, J = 8.0 Hz, 2CH-Ar), 8.28 (d, 2H, J = 7.6 Hz, 2CH-Ar); 13C NMR (CDCl3, 100 MHz): δ ppm 14.0, 32.6, 52.3, 54.0, 60.7, 123.7, 128.3, 130.2, 138.7, 149.6, 164.6, 172.7; IR (KBr, cm−1): 3252, 3066, 2985, 1733, 1656, 1526, 1344, 1191, 631. Anal. Calcld. for C19H23N3O8: C, 53.54; H, 6.08; N, 11.02. Found: C, 53.78; H, 6.21; N, 11.32.

Dibutyl 3,3′-(2-(4-nitrobenzoyl)hydrazine-1,1-diyl)dipropanoate (3e)
White crystal; mp 78–79°C; 1H NMR (CDCl3, 400 MHz): δ ppm 0.88 (t, 6H, J = 7.4 Hz, 2CH3), 1.30 (sextet, 4H, J = 7.4 Hz, 2CH2), 1.53 (quintet, 4H, J = 7.1 Hz, 2CH2), 2.61 (t, 4H, J = 6.5 Hz, 2CH2), 3.30 (t, 4H, J = 6.5 Hz, 2NCH3), 3.99 (t, 4H, J = 6.7 Hz, 2OCH2), 7.54 (s, 1H, NH), 7.95 (d, 2H, J = 8.8 Hz, 2CH2), 8.29 (d, 2H, J = 8.8 Hz, 2CH-Ar); 13C NMR (CDCl3, 100 MHz): δ ppm 12.5, 22.0, 29.5, 31.6, 51.3, 63.7, 122.7, 127.2, 137.7, 148.8, 163.4, 171.8; IR (KBr, cm−1): 3254, 3066, 2960, 1732, 1657, 1525, 1543, 1189, 632. Anal. Calcld. for C30H32N2O10: C, 57.65; H, 7.14; N, 9.60. Found: C, 57.22; H, 7.41; N, 9.27.

Dihexyl 3,3′-(2-(4-nitrobenzoyl)hydrazine-1,1-diyl)dipropanoate (3f)
White solid; mp 79–81°C; 1H NMR (CDCl3, 400 MHz): δ ppm 0.86 (m, 6H, 2CH3), 1.22–130 (m, 12H, 6CH2), 1.50–1.55 (m, 4H, 2CH2), 2.61 (t, 4H, J = 6.5 Hz, 2CH2), 3.30 (t, 4H, J = 6.5 Hz, 2NCH3), 3.98 (t, 4H, J = 6.8 Hz, 2OCH2), 7.56 (s, 1H, NH), 7.95 (d, 2H, J = 8.7 Hz, 2CH-Ar), 8.28 (d, 2H, J = 8.7 Hz, 2CH-Ar); 13C NMR (CDCl3, 100 MHz): δ ppm 12.9, 21.4, 24.4, 27.4, 30.3, 31.6, 51.3, 64.0, 122.7, 127.2, 137.6, 148.7, 163.4, 171.8; IR (KBr, cm−1): 3250, 3035, 2932, 1733, 1657, 1525, 1343, 1187, 633. Anal. Calcld. for C32H36N2O10: C, 60.83; H, 7.96; N, 8.51. Found: C, 60.59; H, 7.65; N, 8.33.

Dipropylbenzamidoaspartate (4h)
Yellow oil; 1H NMR (CDCl3, 400 MHz): δ ppm 0.91 (t, 6H, J = 7.3 Hz, 2CH3) 1.36 (m, 4H, 2CH2), 1.61 (quintet, 4H, J = 7.0 Hz, 2CH2), 1.25 (s, 1H, NH), 2.87 (d, 2H, J = 5.7 Hz, CH2), 4.06–4.11 (m, 2H, OCH2), 4.14–4.21 (m, 2H, OCH2), 5.46 (sbr, 1H, CH); 13C NMR (CDCl3, 100 MHz): δ ppm 12.5, 22.0, 29.5, 31.6, 51.3, 63.7, 122.7, 127.2, 137.7, 148.8, 163.4, 171.8; IR (KBr, cm−1): 3294, 3063, 2960, 1736, 1658, 1180, 694. Anal. Calcld. for C19H27N2O10: C, 62.62; H, 7.74; N, 7.69. Found: C, 62.35; H, 7.49; N, 7.84.
Results and discussion

In this study, we synthesized 12 new compounds via Michael addition reaction of various acyl hydrazides with α,β-unsaturated esters. Firstly, we tried to carry out a model Michael reaction in which n-butyl acrylate 2b was used as a Michael acceptor substrate to react with acyl hydrazide 1a in the presence of TBAB as a strong ionic organic salt at room temperature under solvent-free conditions (Scheme 2).

Initially, this model reaction was examined in the presence of TBAB and diverse organic and inorganic bases at room temperature (Table 1). The model reaction failed with bases Na₂CO₃, SrCO₃ and no base media (Table 1, entries 4, 5, 11). Bases NaHCO₃ and NEt₃ produced only bis-Michael adduct in a trace yields (Table 1, entries 6, 7). Also, in the presence of KOH, NaOH, CaO, CuO, the bis-Michael adduct was produced in low yields (Table 1, entries 1, 2, 8, 9), and in the presence of base K₂CO₃ the product was afforded in a moderate yield (Table 1, entry 3). However, the best yields were obtained when DABCO was used in reaction media under solvent-free conditions (Table 1, entry 10).

We repeated the model reaction under the above conditions with ratio of n-butyl acrylate:benzohydrazide 1a = 2.5:1 (molar ratio).

Table 1. Michael reaction of acylhydrazide 1 (x = H) with n-butyl acrylate in the presence of different bases and TBAB under solvent-free conditions.

| Entry | Basea | Time (h) | Yieldb (%) |
|-------|-------|----------|------------|
| 1     | KOH   | 6        | 15         |
| 2     | NaOH  | 6        | 20         |
| 3     | K₂CO₃ | 6        | 45         |
| 4     | Na₂CO₃| 6        | –          |
| 5     | SrCO₃ | 6        | –          |
| 6     | NaHCO₃| 6        | Trace      |
| 7     | NEt₃  | 6        | Trace      |
| 8     | CaO   | 6        | 15         |
| 9     | CuO   | 6        | 15         |
| 10    | DABCO | 6        | 95         |
| 11    | –     | 6        | –          |

aThe reactions were performed with benzohydrazide (1.0 mmol), base (1.0 mmol) and n-butyl acrylate (2.5 mmol) in tetrabutylammonium bromide (1.0 mmol) at room temperature under solvent-free conditions.

bIsolated yield.

Table 2. The effect of different solvents on aza-Michael reaction of n-butyl acrylate and benzohydrazide at room temperature.

| Entry | Solvent       | Time (h) | Yieldb (%) |
|-------|---------------|----------|------------|
| 1     | DMF           | 24,8     | –          |
| 2     | DMSO          | 24,8     | –          |
| 3     | CHCl₃         | 24,8     | –          |
| 4     | CH₂Cl₂        | 24,8     | –          |
| 5     | MeOH          | 24,8     | 6.8        |
| 6     | EtOH          | 24,8     | 3.3        |
| 7     | CH₃CO₂CH₂CH₃  | 24,8     | –          |
| 8     | H₂O           | 24,8     | –          |
| 9     | TBAB          | 6         | 95         |
| 10    | No solvent    | 24       | –          |

aThe reactions were carried out with acyl hydrazide (1 mmol), DABCO (1 mmol) and n-butyl acrylate (2.5 mmol) in tetrabutylammonium bromide (1 mmol) or 5 mL solvent at room temperature.

bIsolated yield.
1.2 : 1.0. According to stoichiometric equation, this ratio should yield mono-adduct, while based on TLC test in different times after the starting of reaction, bis-adduct was the only afforded product and no mono-Michael product (mono-adduct) was obtained at all. This can be attributed to the fact that the initially produced mono-adduct is a secondary amine. Secondary amines are more nucleophilic than primary amines and thus the mono-adduct reacts faster than benzohydrazide with n-butyl acrylate. Also, we optimized the molar ratio of DABCO and TBAB and showed that a good yield was obtained by employing equimolar of DABCO and TBAB.

In another study, to evaluate the effects of solvents, the model reaction was performed in various solvents at room temperature (Table 2). This reaction was failed in solvents DMF, DMSO, CHCl₃, CH₂Cl₂, ethyl acetate, Table 3. Michael addition of acyl hydrazide 1 to diverse α,β-unsaturated esters at room temperature or 70°C under solvent-free conditions.

| Entry | Acyl hydrazide 1 | Ester 2 | Product | Time (h) | Yield (%) |
|-------|------------------|---------|---------|----------|-----------|
| 1ᵃ    | \( \text{Ph} \) | \( \text{CH}_{2} \text{CH} = \text{CH} \text{COOCH}_{3} \) | \( \text{Ph} \) \( \text{NH} \) \( \text{N} \) \( \text{NH}_{2} \) \( \text{N} \) \( \text{O} \) \( \text{O} \) \( \text{COOCH}_{3} \) | 7 | 95 |
| 2ᵃ    | \( \text{Ph} \) | \( \text{CH}_{2} \text{CH} = \text{CH} \text{COOCH}_{3} \) | \( \text{Ph} \) \( \text{NH} \) \( \text{N} \) \( \text{NH}_{2} \) \( \text{N} \) \( \text{O} \) \( \text{O} \) \( \text{COOCH}_{3} \) | 7 | 95 |
| 3ᵃ    | \( \text{Ph} \) | \( \text{CH}_{2} \text{CH} = \text{CH} \text{COOCH}_{3} \) | \( \text{Ph} \) \( \text{NH} \) \( \text{N} \) \( \text{NH}_{2} \) \( \text{N} \) \( \text{O} \) \( \text{O} \) \( \text{COOCH}_{3} \) | 7 | 90 |
| 4ᵃ    | \( \text{NO}_2 \text{Ph} \) | \( \text{CH}_{2} \text{CH} = \text{CH} \text{COOCH}_{3} \) | \( \text{NO}_2 \text{Ph} \) \( \text{NH} \) \( \text{N} \) \( \text{NH}_{2} \) \( \text{N} \) \( \text{O} \) \( \text{O} \) \( \text{COOCH}_{3} \) | 7 | 95 |
| 5ᵃ    | \( \text{NO}_2 \text{Ph} \) | \( \text{CH}_{2} \text{CH} = \text{CH} \text{COOCH}_{3} \) | \( \text{NO}_2 \text{Ph} \) \( \text{NH} \) \( \text{N} \) \( \text{NH}_{2} \) \( \text{N} \) \( \text{O} \) \( \text{O} \) \( \text{COOCH}_{3} \) | 7 | 95 |
| 6ᵃ    | \( \text{NO}_2 \text{Ph} \) | \( \text{CH}_{2} \text{CH} = \text{CH} \text{COOCH}_{3} \) | \( \text{NO}_2 \text{Ph} \) \( \text{NH} \) \( \text{N} \) \( \text{NH}_{2} \) \( \text{N} \) \( \text{O} \) \( \text{O} \) \( \text{COOCH}_{3} \) | 7 | 90 |
| 7ᵃ    | \( \text{H}_2 \text{NPh} \) | \( \text{CH}_{2} \text{CH} = \text{CH} \text{COOCH}_{3} \) | \( \text{H}_2 \text{NPh} \) \( \text{NH} \) \( \text{N} \) \( \text{NH}_{2} \) \( \text{N} \) \( \text{O} \) \( \text{O} \) \( \text{COOCH}_{3} \) | 7 | 90 |
Having this model reaction in hand, we examined diverse acrylic esters and acyl hydrazides the results of which are summarized in Table 3 (entries 1–7). From this table, it is observed that double aza-Michael addition between acyl hydrazides and acrylic esters led to the production of bis-adducts in excellent yields (90–95%).

Reaction conditions: "The reaction was performed with acyl hydrazides (1.0 mmol), acrilic esters (2.5 mmol), TBAB (1.0 mmol), DABCO (1.0 mmol), at room temperature. "The reaction was performed with acyl hydrazides (1.0 mmol), fumaric esters (1.2 mmol), TBAB (1.0 mmol), DABCO (1 mmol), at 70 °C. "Isolated yield.

water and none solvent media (Table 2, entries 1–4 and 7,8,10). Solvents MeOH, EtOH produced bis-adduct in trace yields (Table 2, entries 5,6). However, in the presence of TBA as a strong ionic organic salt under solvent-free conditions, desired bis-adduct was isolated in an excellent yields (Table 2, entry 9).
The fumaric esters can be considered as derivatives of acrylic esters in which one of the methylenic hydrogen atoms was substituted by alkoxy carbonyl (–COOR) groups. With this idea in our mind, we decided to repeat the model reaction with n-butyl fumarate instead of n-butyl acrylate (Scheme 4). Although TLC test showed no product for the model reaction at room temperature, but with increasing temperature to 70°C it was observed as a surprising phenomenon that this reaction provided mono-adduct 4e as the only product. It can be related to the presence of a bulkiness as well as electron-withdrawing property of butyloxy carbonyl (–COO-n-Bu) group at the β-position of n-butyl fumarate rather than n-butyl acrylate that decrease the nucleophilicity of β-N atom and offer only the first attacking of β-N atom of benzohydrazide. To further investigate, we tested various bases and solvents for the model reaction with n-butyl fumarate. However, the best conditions was using base DABCO in the presence of the organic salt TBAB.

With this established optimum conditions (acyl hydrazide (1.0 mmol), DABCO (1.0 mmol), TBAB (1.0 mmol) and fumaric esters (1.2 mmol)), we were keen to explore the scope of the reaction with respect to other fumaric esters and acyl hydrazides, whose results are depicted in Table 3 (entries 8–12).

It is seen from the results of Table 3 that the reaction proceeded smoothly and afforded the corresponding mono-Michael adducts with isolated yields ranging from 85 to 90% in 10 h. Also, it is observed that the chain length of alkoxy groups do not have considerable effect on the reaction time and efficiency.

Conclusions

In summary, we have developed a novel, efficient and green method for the synthesis of new acyl hydrazide derivatives via reaction of various acyl hydrazides with α,β-unsaturated esters in the presence of TBAB and the organic base DABCO. The reaction products were bis-Michael adducts with acrylic esters at room temperature, but fumaric esters provided mono-Michael adducts at 70°C. Ionic organic salt TBAB is recoverable and available; also the employed base catalyst (DABCO) in this reaction is an inexpensive and available base. Herein, the method as reported will find applications in other areas of research.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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