Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/c8ob02903b

A catalyst-free four-component domino reaction for the synthesis of functionalized 3-acyl-1,5-benzodiazepines†

Yue-Wei Sun, Yue-Ming Bei and Lan-Zhi Wang *

Received 21st November 2018,
Accepted 3rd January 2019

DOI: 10.1039/c8ob02903b

rsc.li/obc

Various functional 3-acyl-1,5-benzodiazepines containing carboxyl, ester and acyl groups at the 2-position were synthesized *via* an efficient, sustainable and catalyst-free domino reaction. During the synthesis process, one new cycle and four new bonds (one C–C, two C–N and one C=C) were constructed by the nucleophilic substitution, nucleophilic addition, dehydration and cyclization reaction by the H^+ shift. Furthermore, a total of 26 examples were examined by reacting inexpensive starting materials of *N*,*N*-dimethylformamide dimethyl acetal, aromatic ketones, 1,2-phenylenediamine compounds and aldehyde derivatives. Therefore, it displayed a broad substrate scope, good functional group tolerance, high yields (77–97%) and the ease of obtaining target compounds without the involvement of toxic solvents and column chromatography, which provided a novel method for the synthesis of a wide variety of biologically relevant 1,5-benzodiazepines.

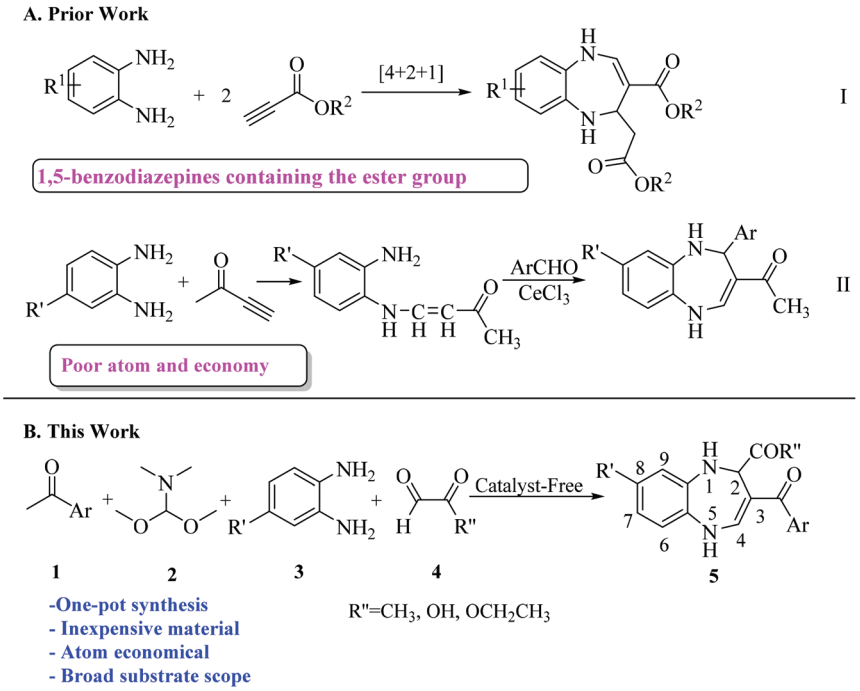
Introduction

Carbon–carbon and carbon–nitrogen bonds are ubiquitously present in most of the natural and synthetic organic molecules, particularly in nitrogen-containing heterocycle frameworks.[1] Benzodiazepines are important classes of nitrogen-containing heterocycles with pharmacological activities, which are broadly used as analgesic, sedative, anticonvulsant, antianxiety and hypnotic agents.[2–4] Over 40 medications highlight benzodiazepines as a classic privileged structure with a broad range of therapeutic treatments. Recently, the results of medical research indicated that benzodiazepines could be extended to various diseases such as cancer, viral infection and cardiovascular disorders.[5] Due to their wide biological activity, the synthesis of these compounds has received a great deal of attention.[6] Consequently, the design of novel reactions with unprecedented procedures for the synthesis of new classes of benzodiazepine-based molecules, as well as for multiple bond (C–C/C=C/C–N) formation using an inexpensive substrate with a simple catalytic system, remains a highly desirable and continuous goal in contemporary organic synthesis.[7,8] In this context, one-pot domino reactions have emerged as a tool to realize the objective due to their efficient atom economy and green characteristics.[9]

The introduction of the pharmacological and physiological active groups including –COOR,[10] –COOH, –COR[11] on the seven-membered ring can bring about some remarkable changes in the reactivity and activity of the new 1,5-benzodiazepins. As far as we know, 1,5-benzodiazepines containing the ester group are investigated widely. For example, in 2010, Jian-Ping Zou[12] *et al.* developed a novel [4 + 2 + 1] cycloaddition reaction to synthesize a new class of 3,4-disubstituted 1,5-benzodiazepines (Scheme 1A-I). However, there is a paucity of reports on the one-pot procedure for the synthesis of 3-acyl-1,5-benzodiazepines from readily available starting materials. Previously, we have established a mild method for the synthesis of 2-aryl-3-acetyl-1,5-benzodiazepines (Scheme 1A-II).[13] Although this method was proved to be successful and allowed facile access to 3-acyl-1,5-benzodiazepines, it suffered from certain disadvantages, such as the need for a highly expensive reagent (3-butyn-2-one) and a limited substrate scope, which makes this strategy less adaptable for the sustainable synthesis. This scenario strongly suggests that the development of a new methodology, which meets the requirements of sustainable chemistry, is still challenging. Continuing our effort on the development of new sustainable protocols to construct 3-acyl-1,5-benzodiazepines, herein, we have developed an efficient and novel approach for the synthesis of highly functionalized 3-acyl-1,5-benzodiazepines **5** (Scheme 1B II) *via* a domino sequence of a nucleophilic substitution/nucleophilic addition/dehydration/cyclization/H^+ shift. These reactions were achieved by reacting aromatic ketones **1**, *N*,*N*-dimethylformamide dimethyl acetal **2**, and

College of Chemistry & Material Science, Hebei Normal University, Shijiazhuang 050024, China. E-mail: wanglanzhi@hebtu.edu.cn

†Electronic supplementary information (ESI) available: IR, MS/MS and NMR spectra. See DOI: 10.1039/c8ob02903b

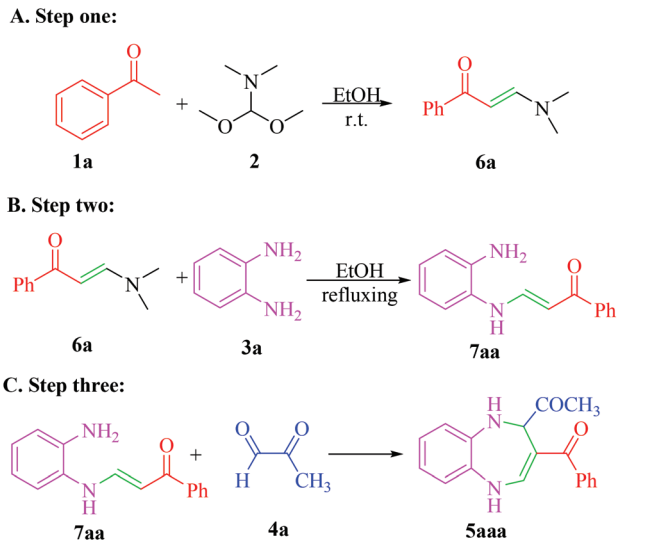


Scheme 1 Synthetic routes to 3-acyl-1,5-benzodiazepines **5**.

1,2-phenylenediamine compounds **3** with aldehyde derivatives **4** without using any metal catalysts. These reactions showed a broad substrate scope and did not require inexpensive commercial starting materials. To the best of our knowledge, this is the first report of the synthesis of 3-acyl-1,5-benzodiazepines with the ester, carboxyl and acyl groups at the 2-position.

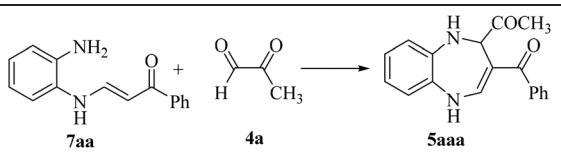
Results and discussion

According to the pathway shown in Scheme 2, a stepwise synthesis of 3-aryl-1,5-benzodiazepine **5aaa** was carried out to search for suitable reaction conditions. Firstly, compound **6a** was synthesized from *N*,*N*-dimethylformamide **2** and acetophenone **1a** in an excellent yield of 98% (Scheme 2A).[14]



Scheme 2 The routes of a stepwise synthesis of 3-acyl-1,5-benzodiazepine **5aaa**.

Table 1 Optimization of reaction conditions[a]



Entry	Temp.	Solvent	Catalysts	Time/h	Yield[b]/%
1	0 °C	EtOH	—	11	69
2	r.t.	EtOH	—	3	90
3	78 °C	EtOH	—	1	44
4	r.t.	PhMe	—	6	40
5	r.t.	MeCN	—	5	60
6	r.t.	EtOAc	—	7	65
7	r.t.	MeOH	—	4.5	90
8	r.t.	EtOH	*p*-TsOH	2	65
9	r.t.	EtOH	L-Pro	2.5	63
10	r.t.	EtOH	HOAc	1.5	45
11	r.t.	EtOH	$CeCl_3$	2.5	60

[a] Reaction conditions: Compound **6** (1 mol), methylglyoxal (1 mol), catalyst (5 mol%), solvent (2 mL), unless otherwise mentioned. [b] Isolated yield.

Subsequently, compound **7aa** was successfully synthesized from compound **6a** and 1,2-phenylenediamine **3a** in an excellent yield of 90% (Scheme 2B).[15]

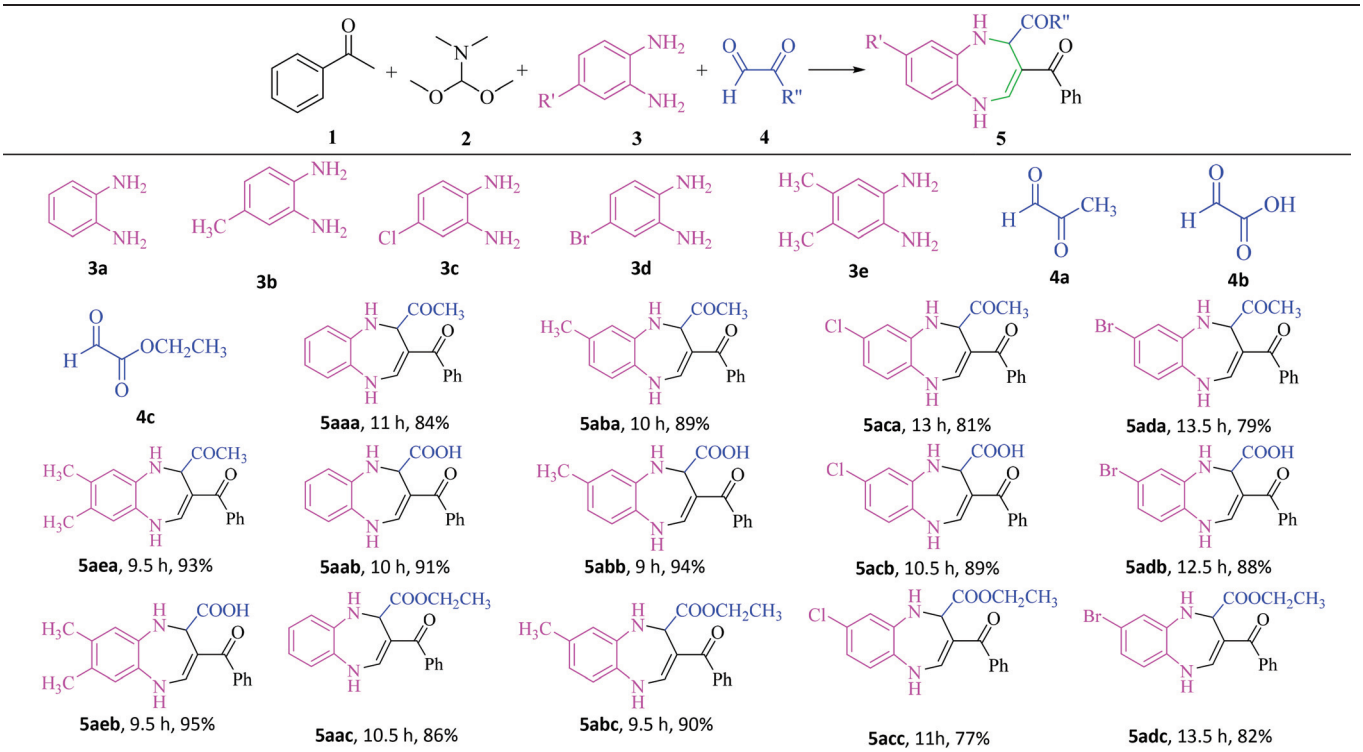
The formation of compound **5aaa** can be reckoned as the crucial step for this work. In order to obtain a high yield of the target compound **5aaa**, the reaction of compound **7aa** and methylglyoxal **4a** was selected as the model reaction (Scheme 2C). The above model reaction was conducted to investigate the impact of various reaction conditions on the reaction outcome, including catalysts, solvents and temperature. These results are listed in Table 1.

To begin with, the effect of the reaction temperature was examined (Table 1, entries 1–3). A screening of different reaction temperatures showed that the reaction gave the best result at room temperature (Table 1, entry 2). Decreasing reaction temperature slowed down the reaction rate (Table 1, entry 1). Increasing the reaction temperature decreased the yield because side products were produced by TLC (Table 1, entry 3). Next, various solvents, such as methanol, ethanol, toluene, acetonitrile and ethyl acetate, were employed as reaction media. The solvents exhibited great influence on the reaction rate. Among these solvents, the protic solvents resulted in product **5aaa** in higher isolated yields. Methanol gave good yields but needed longer reaction time than ethanol (Table 1, entries 2 and 7). In terms of yield and reactivity, ethanol was the most suitable reaction medium. A lower yield of product **5aaa** was obtained when the reaction was performed in different aprotic solvents (Table 1, entries 4–6). Finally, the catalyst was examined. The reaction was proceeded smoothly without acidic promoters to give 1,5-benzodiazepine **5aaa** in excellent yield (Table 1, entry 2). Then, different acids were screened for this reaction. Unfortunately, when various acidic catalysts were evaluated as potential promoters for this reaction, the desired product was obtained only in yields of 45%–65% (Table 1, entries 8–11). Consequently, the following reaction conditions are recommended: catalyst-free in ethanol at room temperature (Table 1, entry 2).

With the optimized reaction conditions in hand, we attempted a green domino process for the one-pot synthesis of 1,5-benzodiazepine **5aaa** (Scheme 3) of *N*,*N*-dimethylformamide dimethyl acetal **2**, acetophenone **1a**, 1,2-phenylenediamine **3a** and methylglyoxal **4a**. To our delight, this domino reaction proceeded smoothly to give 1,5-benzodiazepine **5aaa**

Scheme 3 One-pot synthesis of 1,5-benzodiazepine *via* a domino reaction.

Table 2 Scope of 1,2-phenylenediamin and aldehyde derivatives for one-pot synthesis of benzodiazepines[a]



[a] Reaction conditions: *N*,*N*-Dimethylformamide dimethyl acetal (1 mmol), acetophenone (1 mmol), 1,2-phenylenediamine compounds (1 mmol), and aldehyde derivatives (1 mmol) in EtOH (2 ml), reflux to rt.

in good yield (84%). This encouraging result indicated the feasibility of the envisioned domino reaction.

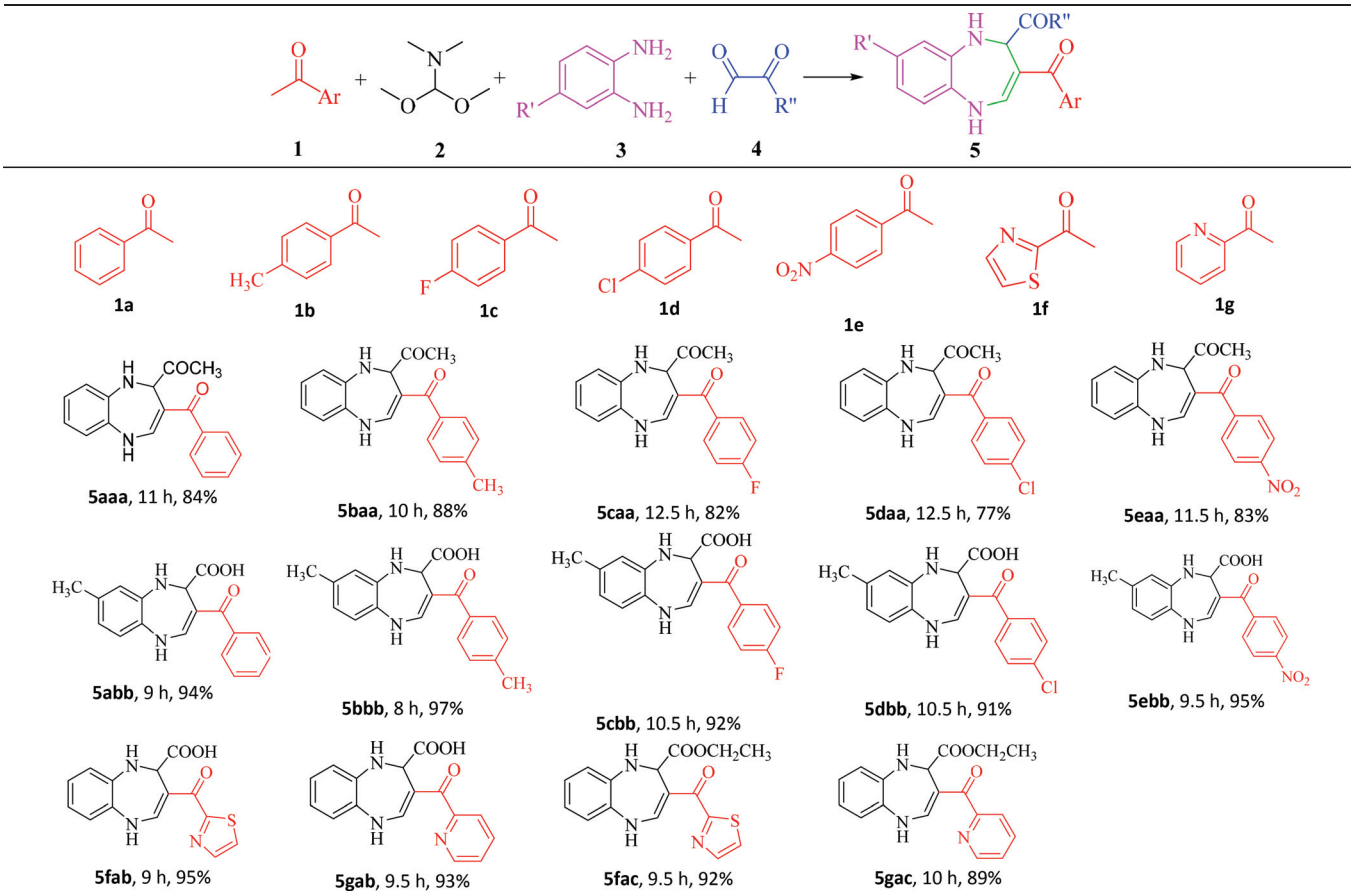
Therefore, the generality and limitation of this domino approach were examined. Initially, we evaluated the reaction scope with different substituted 1,2-phenylenediamines **3a–e**. As shown in Table 2, the different substituted 1,2-phenylenediamine compounds were well tolerated. These reactions gave good to excellent yields of desired product **5**. Importantly, we observed that electron-rich 1,2-phenylenediamine compounds were more reactive. Thus, these reactions gave better yields than those possessing electron withdrawing groups. Then, as an extension of the above study, we chose a variety of aldehyde derivatives **4a–c** to react to investigate the possibility of this reaction. As anticipated, these reactions proceeded smoothly to give corresponding 1,5-benzodiazepines in good to excellent yields.

Furthermore, we set out to explore the scope with different aromatic ketone derivatives **1** (Table 3). From the results, when 4′-methylacetophenone **1b** bearing electron donating groups was tested, these reactions furnished desired products in 88–97% yield. When moderate electron withdrawing groups such as chlorine and fluorine were introduced at the *para*-position of acetophenone, the expected products **5caa–5daa** and **5cbb–5dbb** were also achieved in good yields of 77–92%. Pleasingly, acetophenone with a strong electron withdrawing group on the phenyl ring, such as $-NO_2$, afforded the 1,5-benzodiazepines **5eaa** and **5ebb** in yields of 83–95%. Encouraged by these results, we decided to further explore the scope of aromatic ketone derivatives. 2-Acetylthiazole **1f** and 2-acetylpyridine **1g** were desirable substrates for this reaction to afford the corresponding products **5fab–5gab** and **5fac–5gac** in excellent yields of 89–95%. This result can be attributed to higher reactivity of 2-acetylthiazole **1f** and 2-acetylpyridine **1g** than that of acetophenone **1a**.

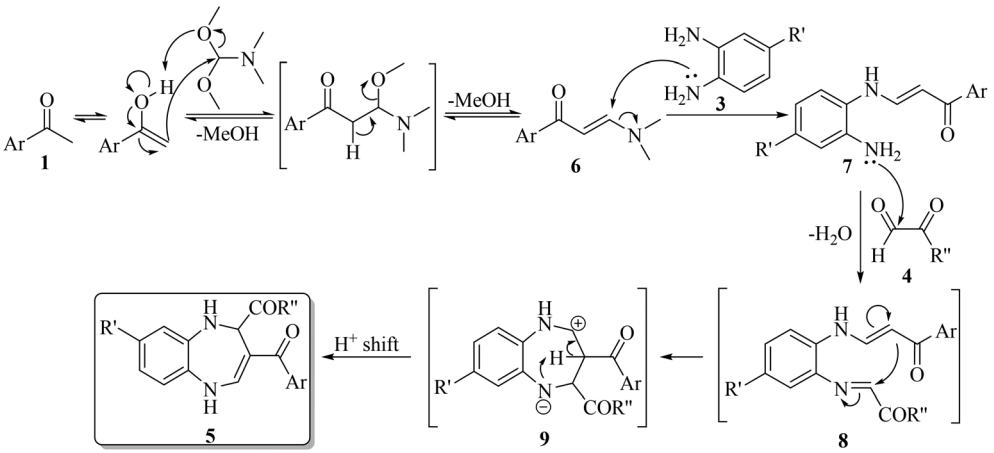
As summarized in Tables 2 and 3, this new domino approach tolerates a wide range of substituents on the 1,5-benzodiazepines. The functional groups include carboxyl, ester and acyl groups at the 2-position on the seven-membered ring, and a series of aryl groups on the 3-acyl and various substituents on the benzene ring.

On the basis of the above results, the plausible mechanism is depicted in Scheme 4. Firstly, the compound **6** was obtained by two nucleophilic substitution reactions of enolized aromatic ketone **1** and *N*,*N*-dimethylformamide dimethyl acetal **2** with

Table 3 Scope of aromatic ketones for one-pot synthesis of 1,5-benzodiazepines[a]



[a] Reaction conditions: *N*,*N*-Dimethylformamide dimethyl acetal (1 mmol), aromatic ketones (1 mmol), 1,2-phenylenediamine compounds (1 mmol), and aldehyde derivatives (1 mmol) in EtOH (2 ml), reflux to rt.



Scheme 4 Plausible mechanism for the formation of 1,5-benzodiazepine **5**.

the removal of the methanol molecules. Then, nucleophilic substitution of the active amino group of substituted 1,2-phenylenediamine **3** onto the nitrogen atom of compound **6** leads to the formation of intermediate **7**. This step has a very high selectivity. Subsequently, the other amino group of intermediate **7** attacks the electrophilic carbonyl carbon of aldehyde derivatives **4** to give the corresponding intermediate **8** *via* a nucleophilic addition–dehydration reaction. Adduct **8** undergoes intramolecular cyclization enabling the cyclic intermediate **9**, which suffers intramolecular proton transfer to give the product **5**.

When the asymmetric 1,2-phenylenediamine compounds were used as the substrate, selectivity of the position of R′ may exist. But only single isomers **7** were obtained in the experiment. Previously, a similar structure of 1,5-benzodiazepines (Scheme 1A-II) was confirmed by X-ray diffraction.[13] The result shows that the isomer formed is similar in both cases. To further prove the structure of products **7**, quantum chemical calculations were performed and DFT studies based on the B3LYP method and 6-31G basis set were employed to carry out the study.

To start with, NBO charge analysis of the substituted 1,2-phenylenediamine **3b–3d** was carried out to justify the selective attack at the nucleophilic centers (N1 and N2). The results are summarized in Table 4. The NBO charge analysis reveals that N1 and N2 are negatively charged. However, the charge density of N1 is significantly higher than that of N2. N1 of substituted 1,2-phenylenediamine is very strongly nucleophilic (hard nucleophilic) compared to N2 (soft nucleophilic). The N1 of substituted 1,2-phenylenediamine attacks the compound **6** to give the corresponding compound **7** *via* a nucleophilic substitution reaction. This result verifies the rationality of the mechanism proposed in this paper.

Furthermore, the compounds **7** obtained in this reaction and the corresponding isomers **10** were analyzed for zero-point energy, thermodynamic energy, thermodynamic enthalpy and Gibbs free energy (Table 5). Since the structures of products **7** are different from the structures of compounds **10**, the calculation of the respective energy parameters is also different. The lower the energy, the more stable the structure. Considering that products **7ab–7ad** were more stable than those of isomers **10ab–10ad**, the selective formation of predominant products **7ab–7ad** from the reaction of **3b–3d** with **6a** is justified on thermodynamic grounds. This result also verifies the rationality of the mechanism proposed in this paper.

Table 4 Calculated NBO Charges of Optimized substituted 1,2-phenylenediamine compounds **3b–3d**

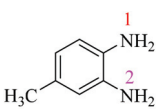
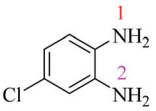
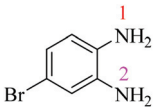
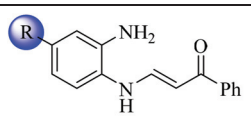
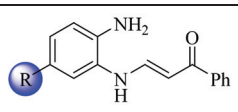
	 **3b**	 **3c**	 **3d**
N1	−0.87425	−0.89655	−0.87002
N2	−0.87029	−0.89506	−0.86700

Table 5 Zero-point energies, values of thermal energies, thermodynamic enthalpy and Gibbs free energies of **7ab–7ad** and **10ab–10ad**



7ab: R=CH_3
7ac: R=Cl
7ad: R=Br



10ab: R=CH3
10ac: R=Cl
10ad: R=Br

Comp.	E_{zp}/a.u.	$E^{\neq}/10^3$ kJ mol^{-1}	$H^{\neq}/10^3$ kJ mol^{-1}	$G^{\neq}/10^3$ kJ mol^{-1}
7ab	−803.8051	−2110.3443	−2110.3419	−2110.5165
10ab	−803.8046	−2110.3427	−2110.3402	−2110.5166
7ac	−1224.1156	−3213.8711	−3113.8686	−3214.0404
10ac	−1224.1149	−3213.8694	−3213.8669	−3214.0384
7ad	−3335.6250	−8757.6384	−8757.6359	−8757.8112
10ad	−3335.6245	−8757.6371	−8757.6346	−8757.8104

In summary, the structural assignment and computational results are in agreement with previous papers[13,16] in which a similar reaction was performed.

Conclusions

In conclusion, we have developed a catalyst-free and unprecedented strategy for one-pot synthesis of diverse novel 3-acyl-1,5-benzodiazepines, which provides a domino reaction of *N*,*N*-dimethylformamide dimethyl acetal, aromatic ketones, 1,2-phenylenediamine and aldehyde derivatives. Moreover, the reaction simultaneously installs one C–C bond, two C–N bonds and one C=C bond to form one new seven-membered ring, which resulted in the synthesis of highly functionalized 3-acyl-1,5-benzodiazepines containing carboxyl, ester and acyl groups at the 2-position. The salient features of this methodology include the use of inexpensive and easily available starting materials, convenient one-pot operation, ease of product purification and good yields. Significantly, the protocol showed a broad substrate scope and outstanding functional group tolerance. The novel 1,5-benzodiazepines provide a collection of promising compounds with structural diversity for future bioassays and medical treatments.

Experimental section

Materials and methods

Melting points were determined in open capillaries and were uncorrected. The ^{1}H NMR and ^{13}C NMR spectral analyses were performed on a 400 MHz (WIPM-NMR-400) nuclear magnetic resonance spectrometer operating at 400/500 and 100/125 MHz, respectively, in DMSO-d_6 with the chemical shift given in parts per million relative to tetramethylsilane (TMS) as the internal standard. The signal multiplicities are represented by s (singlet), d (doublet), t (triplet), m (multiplet), and q (quartet). The IR spectra were recorded on a Thermo SCIENTIFIC IR spectrophotometer in KBr pellets and reported in cm^{-1}. The elemental analysis (C, H, N) was performed with a VarioELIII Elemental Analyser. Low-resolution mass spectra were recorded on a Thermo DSQ II mass spectrometer. Synthetic grade chemicals were purchased from Aladdin and were used as received. The solvents were commercial products of analytical grade and dried according to the literature as necessary. The reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel GF254 plates.

General methods

Synthesis of 3-acyl-1,5-benzodiazepine derivatives **5**.

Firstly, the reaction was carried out by taking a 1 : 1 mol ratio mixture of *N*,*N*-dimethylformamide **2** (1 mmol) and aromatic ketones **1** (1 mmol) in ethanol (2 mL) in a 50 mL round bottom flask with stirring at refluxing ethanol for 1 h, with TLC showing the formation of a single product **6**. Subsequently, the 1,2-phenylenediamine **3** (1 mmol) was added to the reaction mixture and stirred in refluxing ethanol. The whole process takes 6 h. Finally, the aldehyde derivatives **4** (1 mmol) were added to the reaction mixture and stirred at room temperature. Upon completion, as monitored by TLC, the solid **5** was crystallised at 0 °C and the resulting solid was washed with ethanol.

3-Acyl-1,5-benzodiazepine 5aaa

Yellow solid; 245 mg, 84%; Mp: 188–189 °C; IR (KBr): 3330 (NH), 1704 (C=C), 1635 (C=O), 1540 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, TMS): δ 2.14 (3H, s, Me), 5.24 (1H, d, J = 4.0 Hz, CH), 6.52 (1H, d, J = 4.0 Hz, NH), 6.71–6.88 (4H, m, Ph), 7.10 (1H, d, J = 6.4 Hz, CH), 7.46 (5H, s, Ph), 9.52 (1H, d, J = 6.4 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ 28.7, 63.0, 120.3, 120.6, 120.9, 123.9, 128.6, 130.2, 138.5, 140.7, 146.7, 192.9, 205.8; found C, 73.87; H, 5.36; N, 9.74%; M + 1 (mass spectrum), 293.2. $C_{18}H_{16}N_2O_2$ requires C, 73.95; H, 5.52; N, 9.58%; M, 292.34.

3-Acyl-1,5-benzodiazepine 5aba

Pale yellow solid; 272 mg, 89%; Mp: 168–170 °C; IR (KBr): 3334 (NH), 1702 (C=C), 1635 (C=O), 1538 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, TMS): δ 2.14 (3H, s, Me), 2.17 (3H, s, Me), 5.22 (1H, d, J = 2.4 Hz, CH), 6.44 (1H, d, J = 2.4 Hz, NH), 6.53–6.70 (3H, m, Ph), 7.08 (1H, d, J = 5.6 Hz, CH), 7.46 (5H, s, Ph), 9.48 (1H, d, J = 6.0 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ 20.8, 28.7, 62.8, 110.1, 120.5, 121.1, 127.7, 128.6, 130.1, 132.9, 138.3, 140.8, 146.6, 192.6, 205.8; found C, 74.38; H, 5.69; N, 9.22%; M + 1 (mass spectrum), 307.2. $C_{19}H_{18}N_2O_2$ requires C, 74.49; H, 5.92; N, 9.14%; M, 306.37.

3-Acyl-1,5-benzodiazepine 5aca

Yellow solid; 264 mg, 81%; Mp: 186–188 °C; IR (KBr): 3340 (NH), 1702 (C=C), 1635 (C=O), 1527 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, TMS): δ 2.16 (3H, s, Me), 5.29 (1H, d, J = 5.6 Hz, CH), 6.69 (1H, d, J = 5.6 Hz, NH), 6.73–6.92 (3H, m, Ph), 7.09 (1H, d, J = 8.0 Hz, CH), 7.47 (5H, s, Ph), 9.64 (1H, d, J = 8.0 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ 28.8, 62.6, 110.5, 119.5, 119.6, 121.8, 127.2, 128.5, 128.6, 128.9, 130.3, 140.0, 140.5, 146.2, 192.9, 205.6; found C, 66.24; H, 4.79; N, 8.46%; M + 1 (mass spectrum), 327.2. $C_{18}H_{15}ClN_2O_2$ requires C, 66.16; H, 4.63; N, 8.57%; M, 326.78.

3-Acyl-1,5-benzodiazepine 5ada

Light yellow solid; 293 mg, 79%; Mp: 181–183 °C; IR (KBr): 3337 (NH), 1700 (C=C), 1644 (C=O), 1528 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, TMS): δ 2.19 (3H, s, Me), 5.31 (1H, d, J = 5.6 Hz, CH), 6.76 (1H, d, J = 5.6 Hz, NH), 6.81–7.13 (3H, m, Ph), 7.09 (1H, d, J = 7.6 Hz, CH), 7.50 (5H, s, Ph), 9.85 (1H, d, J = 6.4 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ 28.8, 62.5, 110.4, 115.1, 122.2, 122.2, 122.4, 128.5, 128.6, 129.4, 130.3, 140.4, 140.5, 146.2, 192.8, 205.7; found C, 58.31; H, 4.21; N, 7.41%; M + 1 (mass spectrum), 372.2. $C_{18}H_{15}BrN_2O_2$ requires C, 58.24; H, 4.07; N, 7.55%; M, 371.23.

3-Acyl-1,5-benzodiazepine 5aea

Deep yellow solid; 299 mg, 93%; Mp: 179–180 °C; IR (KBr): 3334 (NH), 1696 (C═C), 1635 (C═O), 1527 (C═O) cm^{-1}; ^1H NMR 400 MHz, DMSO-d_6, (TMS): δ 2.05 (3H, s, Me), 2.08 (3H, s, Me), 2.12 (3H, s, Me), 5.18 (1H, d, J = 5.6 Hz, CH), 6.31 (1H, d, J = 5.6 Hz, NH), 6.55–6.63 (2H, m, Ph), 7.06 (1H, d, J = 8.0 Hz, CH), 7.45 (5H, s, Ph), 9.38 (1H, d, J = 8.0 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ 18.8, 19.2, 28.7, 63.0, 110.3, 121.4, 121.8, 127.8, 127.9, 128.5, 128.6, 130.0, 131.7, 135.9, 140.9, 146.7, 192.6, 205.8; found C, 74.89; H, 6.11; N, 8.88%; M + 1 (mass spectrum), 321.2. $C_{20}H_{20}N_2O_2$ requires C, 74.98; H, 6.29; N, 8.74%; M, 320.3.

3-Acyl-1,5-benzodiazepine 5aab

Yellow solid; 268 mg, 91%; Mp: 177–179 °C; IR (KBr): 3333 (NH), 1684 (C═C), 1639 (C═O), 1534 (C═O) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, TMS): δ 5.15 (1H, d, J = 5.0 Hz, CH), 6.32 (1H, d, J = 5.0 Hz, NH), 6.73–6.89 (4H, m, Ph), 7.05 (1H, d, J = 8.5 Hz, CH), 7.45–7.48 (5H, m, Ph), 9.47 (1H, d, J = 8.0 Hz, NH), 12.23 (1H, s, COOH); ^{13}C NMR (125 MHz, DMSO-d_6, TMS): δ 57.7, 111.4, 120.4, 120.6, 121.5, 123.7, 128.5, 128.6, 130.2, 130.7, 138.9, 140.8, 146.6, 172.9, 192.7; found C, 69.41; H, 4.74; N, 9.49%; M + 1 (mass spectrum), 295.2. $C_{17}H_{14}N_2O_3$ requires C, 69.38; H, 4.79; N, 9.52%; M, 294.31.

3-Acyl-1,5-benzodiazepine 5abb

Pale yellow solid; 290 mg, 94%; Mp: 189–190 °C; IR (KBr): 3325 (NH), 1717 (C═C), 1637 (C═O), 1518 (C═O) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, TMS): δ 2.17 (3H, s, Me), 5.16 (1H, d, J = 4.0 Hz, CH), 6.25 (1H, d, J = 4.5 Hz, NH), 6.56–6.72 (3H, m, Ph), 7.05 (1H, d, J = 8.5 Hz, CH), 7.45–7.48 (5H, m, Ph), 9.43 (1H, d, J = 8.5 Hz, NH), 12.22 (1H, s, COOH); ^{13}C NMR (125 MHz, DMSO-d_6, TMS): δ 20.8, 57.6, 111.0, 120.4, 121.4, 121.7, 128.3, 128.5, 128.6, 130.1, 132.7, 138.7, 140.9, 146.6, 172.9, 192.5; found C, 70.26; H, 5.32; N, 8.89%; M + 1 (mass spectrum), 309.2. $C_{18}H_{16}N_2O_3$ requires C, 70.12; H, 5.23; N, 9.09%; M, 308.34.

3-Acyl-1,5-benzodiazepine 5acb

Purple solid; 292 mg, 89%; Mp: 204–206 °C; IR (KBr): 3318 (NH), 1709 (C═C), 1645 (C═O), 1534 (C═O) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, TMS): δ 5.16 (1H, d, J = 5.5 Hz, CH), 6.60 (1H, d, J = 5.5 Hz, NH), 6.77–6.93 (3H, m, Ph), 7.03 (1H, d, J = 8.0 Hz, CH), 7.45–7.49 (5H, m, Ph), 9.57 (1H, d, J = 8.0 Hz, NH), 12.36 (1H, s, COOH); ^{13}C NMR (125 MHz, DMSO-d_6, TMS): δ 57.4, 111.5, 120.0, 120.3, 121.7, 127.0, 128.6, 128.6, 129.7, 130.3, 140.3, 140.6, 146.0, 172.7, 192.7; found C, 62.25; H, 4.11; N, 8.39%; M + 1 (mass spectrum), 329.2. $C_{17}H_{13}ClN_2O_3$ requires C, 62.11; H, 3.99; N, 8.52%; M, 328.75.

3-Acyl-1,5-benzodiazepine 5adb

Yellow solid; 327 mg, 88%; Mp: 200–202 °C; IR (KBr): 3302 (NH), 1725 (C═C), 1645 (C═O), 1549 (C═O) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, TMS): δ 5.17 (1H, d, J = 5.5 Hz, CH), 6.60 (1H, d, J = 5.5 Hz, NH), 6.76–7.06 (3H, m, Ph), 7.08 (1H, d, J = 8.0 Hz, CH), 7.45–7.50 (5H, m, Ph), 9.57 (1H, d, J = 8.0 Hz, NH), 12.38 (1H, s, COOH); ^{13}C NMR (125 MHz, DMSO-d_6, TMS): δ 57.5, 111.6, 115.0, 122.0, 122.9, 123.2, 128.6, 128.6, 130.1, 130.3, 140.5, 140.6, 146.0, 172.6, 192.7; found C, 54.66; H, 3.39; N, 7.65%; M + 1 (mass spectrum), 373.1. $C_{17}H_{13}BrN_2O_3$ requires C, 54.71; H, 3.51; N, 7.51%; M, 372.21.

3-Acyl-1,5-benzodiazepine 5aeb

Yellow solid; 306 mg, 95%; Mp: 191–193 °C; IR (KBr): 3357 (NH), 1749 (C═C), 1621 (C═O), 1502 (C═O) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, TMS): δ 2.06 (3H, s, Me), 2.08 (3H, s, Me), 5.11 (1H, d, J = 5.0 Hz, CH), 6.05 (1H, d, J = 5.5 Hz, NH), 6.57–6.65 (2H, m, Ph), 7.02 (1H, d, J = 8.5 Hz, CH), 7.42–7.48 (5H, m, Ph), 9.32 (1H, d, J = 8.5 Hz, NH), 12.12 (1H, s, COOH); ^{13}C NMR (125 MHz, DMSO-d_6, TMS): δ 18.9, 19.2, 57.8, 111.1, 121.3, 122.6, 128.2, 128.3, 128.5, 128.6, 130.0, 131.5, 136.5, 141.0, 146.7, 172.9, 192.6; found C, 70.68; H, 5.49; N, 8.73%; M + 1 (mass spectrum), 323.3. $C_{19}H_{18}N_2O_3$ requires C, 70.79; H, 5.63; N, 8.69%; M, 322.36.

3-Acyl-1,5-benzodiazepine 5aac

Pale yellow solid; 277 mg, 86%; Mp: 90–92 °C; IR (KBr): 3333 (NH), 1709 (C═C), 1637 (C═O), 1526 (C═O) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, TMS): δ 0.98 (3H, t, J = 7.0, Me), 3.93 (2H, q, J = 6.5, CH_2), 5.22 (1H, d, J = 5.5 Hz, CH), 6.43 (1H, d, J = 5.5 Hz, NH), 6.76–6.89 (4H, m, Ph), 7.09 (1H, d, J = 8.0 Hz, CH), 7.46–7.46 (5H, m, Ph), 9.51 (1H, d, J = 8.0 Hz, NH); ^{13}C NMR (125 MHz, DMSO-d_6, TMS): δ 14.6, 57.7, 60.6, 110.8, 120.4, 120.9, 121.5, 123.8, 128.5, 128.6, 130.2, 131.0, 138.5, 140.7, 146.7, 171.3, 192.5; found C, 70.83; H, 5.69; N, 8.61%; M + 1 (mass spectrum), 323.2. $C_{19}H_{18}N_2O_3$ requires C, 70.79; H, 5.63; N, 8.69%; M, 322.36.

3-Acyl-1,5-benzodiazepine 5abc

Pale yellow solid; 302 mg, 90%; Mp: 94–96 °C; IR (KBr): 3333 (NH), 1717 (C═C), 1637 (C═O), 1541 (C═O) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, TMS): δ 1.00 (3H, t, J = 6.0, Me), 2.17 (3H, s, Me), 3.94 (2H, q, J = 6.0, CH_2), 5.21 (1H, d, J = 5.5 Hz, CH), 6.33 (1H, d, J = 6.0 Hz, NH), 6.58–6.74 (3H, m, Ph), 7.07 (1H, d, J = 8.0 Hz, CH), 7.45–7.49 (5H, m, Ph), 9.46 (1H, d, J = 8.0 Hz, NH); ^{13}C NMR (125 MHz, DMSO-d_6, TMS): δ 14.6, 20.8, 57.6, 60.5, 110.5, 120.4, 121.6, 121.7, 128.4, 128.5, 128.6, 130.1, 132.8, 138.3, 140.9, 146.6, 171.4, 192.3; found C, 71.53; H, 6.11; N, 8.17%; M + 1 (mass spectrum), 337.2. $C_{20}H_{20}N_2O_3$ requires C, 71.41; H, 5.99; N, 8.33%; M, 336.39.

3-Acyl-1,5-benzodiazepine 5acc

Purple solid; 259 mg, 77%; Mp: 100–102 °C; IR (KBr): 3322 (NH), 1715 (C═C), 1640 (C═O), 1549 (C═O) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, TMS): δ 1.03 (3H, t, J = 6.5, Me), 3.99 (2H, q, J = 6.5, CH_2), 5.24 (1H, d, J = 5.0 Hz, CH), 6.69 (1H, d, J = 4.5 Hz, NH), 6.79–7.09 (3H, m, Ph), 6.95 (1H, d, J = 8.0 Hz, CH), 7.47 (5H, m, Ph), 9.62 (1H, d, J = 7.5 Hz, NH); ^{13}C NMR (125 MHz, DMSO-d_6, TMS): δ 14.6, 57.4, 60.8, 110.9, 120.3, 120.4, 121.7, 127.1, 128.5, 128.6, 129.9, 130.3, 139.9, 140.5, 146.1, 171.1, 192.5; found C, 63.82; H, 4.67; N, 7.99%; M + 1

(mass spectrum), 357.2. $C_{19}H_{17}ClN_2O_3$ requires C, 63.96; H, 4.80; N 7.85%; M, 356.81.

3-Acyl-1,5-benzodiazepine 5adc

Yellow solid; 328 mg, 82%; Mp: 102–104 °C; IR (KBr): 3286 (NH), 1716 (C═C), 1637 (C═O), 1549 (C═O) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, TMS): δ 0.97 (3H, t, J = 6.5, Me), 3.93 (2H, q, J = 6.5, CH_2), 5.18 (1H, d, J = 5.0 Hz, CH), 6.63 (1H, d, J = 4.5 Hz, NH), 6.79–7.03 (3H, m, Ph), 6.89 (1H, d, J = 8.0 Hz, CH), 7.41 (5H, m, Ph), 9.56 (1H, d, J = 7.0 Hz, NH); ^{13}C NMR (125 MHz, DMSO-d_6, TMS): δ 14.6, 57.4, 60.8, 111.0, 115.1, 122.0, 123.2, 123.3, 128.5, 128.6, 130.3, 130.3, 140.2, 140.5, 146.1, 171.1, 192.5; found C, 56.76; H, 4.12; N, 7.11%; M + 1 (mass spectrum), 403.1. $C_{19}H_{17}BrN_2O_3$ requires C, 56.87; H, 4.27; N, 6.98%; M, 402.04.

3-Acyl-1,5-benzodiazepine 5baa

Pale yellow solid; 269 mg, 88%; Mp: 193–194 °C; IR (KBr): 3334 (NH), 1702 (C═C), 1635 (C═O), 1533 (C═O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, TMS): δ 2.14 (3H, s, Me), 2.36 (3H, s, Me), 5.22 (1H, d, J = 5.6 Hz, CH), 6.49 (1H, d, J = 5.6 Hz, NH), 6.70–6.87 (4H, m, Ph), 7.11 (1H, d, J = 8.0 Hz, CH), 7.25–7.38 (4H, m, Ph), 9.45 (1H, d, J = 8.0 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ 21.4, 28.7, 63.1, 110.6, 120.3, 120.8, 123.8, 128.7, 129.1, 130.2, 137.8, 138.4, 139.9, 146.3, 192.8, 205.7; found C, 74.63; H, 6.07; N, 9.01%; M + 1 (mass spectrum), 307.2. $C_{19}H_{18}N_2O_2$ requires C, 74.49; H, 5.92; N, 9.14%; M, 306.37.

3-Acyl-1,5-benzodiazepine 5caa

Pale yellow solid; 254 mg, 82%; Mp: 192–194 °C; IR (KBr): 3328 (NH), 1696 (C═C), 1642 (C═O), 1538 (C═O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, TMS): δ 2.14 (3H, s, Me), 5.23 (1H, d, J = 5.6 Hz, CH), 6.52 (1H, d, J = 5.2, NH), 6.73–6.86 (4H, m, Ph), 7.09 (1H, d, J = 8.4 Hz, CH), 7.26–7.54 (4H, m, Ph), 9.54 (1H, d, J = 8.0 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ 28.6, 63.1, 110.5, 115.4, 115.6, 120.2, 120.6, 120.9, 123.9, 130.1, 131.0, 131.1, 137.1, 137.1, 138.4, 146.6, 162.1, 164.5, 191.6, 205.7; found C, 69.80; H, 4.92; N, 8.88%; M + 1 (mass spectrum), 311.2. $C_{18}H_{15}FN_2O_2$ requires C, 69.67; H, 4.87; N, 9.03%; M, 310.33.

3-Acyl-1,5-benzodiazepine 5daa

Yellow solid; 251 mg, 77%; Mp: 195–196 °C; IR (KBr): 3340 (NH), 1702 (C═C), 1635 (C═O), 1533 (C═O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, TMS): δ 2.14 (3H, s, Me), 5.22 (1H, d, J = 5.6 Hz, CH), 6.54 (1H, d, J = 6.0 Hz, NH), 6.71–6.88 (4H, m, Ph), 7.07 (1H, d, J = 8.0 Hz, CH), 7.48–7.54 (4H, m, Ph), 9.57 (1H, d, J = 8.0 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ 28.6, 63.0, 110.59, 120.3, 120.6, 120.9, 124.0, 128.7, 130.0, 130.5, 134.9, 138.4, 139.4, 146.7, 191.6, 205.6; found C, 66.33; H, 4.87; N, 8.46%; M + 1 (mass spectrum), 327.2. $C_{18}H_{15}ClN_2O_2$ requires C, 66.16; H, 4.63; N, 8.57%; M, 326.78.

3-Acyl-1,5-benzodiazepine 5eaa

Tangerine solid; 280 mg, 83%; Mp: 191–192 °C; IR (KBr): 3334 (NH), 1702 (C═C), 1635 (C═O), 1533 (C═O) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, TMS): δ 2.15 (3H, s, Me), 5.27 (1H, d, J = 4.8 Hz, CH), 6.59 (1H, d, J = 5.6 Hz, NH), 6.83–6.89 (4H, m, Ph), 7.02 (1H, d, J = 8.0 Hz, CH), 7.71–8.31 (4H, m, Ph), 9.71 (1H, d, J = 8.4 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ 28.6, 62.8, 110.5, 120.4, 120.8, 120.9, 123.9, 124.3, 129.7, 129.7, 138.6, 146.9, 147.4, 148.3, 190.6, 205.5; found C, 63.95; H, 4.32; N, 12.56%; M + 1 (mass spectrum), 338.2. $C_{18}H_{15}N_3O_4$ requires C, 64.09; H, 4.48; N, 12.46%; M, 337.34.

3-Acyl-1,5-benzodiazepine 5bbb

Pale yellow solid; 312 mg, 97%; Mp: 200–202 °C; IR (KBr): 3357 (NH), 1709 (C═C), 1605 (C═O), 1573 (C═O) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, TMS): δ 2.18 (3H, s, Me), 2.37 (3H, s, Me), 5.14 (1H, d, J = 4.5 Hz, CH), 6.21 (1H, d, J = 4.5 Hz, NH), 6.56–6.73 (3H, m, Ph), 7.07 (1H, d, J = 8.0 Hz, CH), 7.26–7.38 (4H, m, Ph), 9.38 (1H, d, J = 8.5 Hz, NH), 12.19 (1H, s, COOH); ^{13}C NMR (125 MHz, DMSO-d_6, TMS): δ 20.8, 21.4, 57.7, 110.9, 120.3, 121.3, 121.7, 128.3, 128.7, 129.1, 132.6, 138.0, 138.7, 139.9, 146.3, 172.9, 192.5; found C, 70.74; H, 5.59; N, 8.73%; M + 1 (mass spectrum), 323.3. $C_{19}H_{18}N_2O_3$ requires C, 70.79; H, 5.63, N, 8.69%; M, 322.36.

3-Acyl-1,5-benzodiazepine 5cbb

Yellow solid; 300 mg, 92%; Mp: 196–198 °C; IR (KBr): 3357 (NH), 1717 (C═C), 1629 (C═O), 1597 (C═O) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, TMS): δ 2.18 (3H, s, Me), 5.15 (1H, d, J = 2.5 Hz, CH), 6.24 (1H, d, J = 1.5 Hz, NH), 6.57–6.75 (3H, m, Ph), 7.05 (1H, d, J = 8.0 Hz, CH), 7.27–7.55 (4H, m, Ph), 9.46 (1H, d, J = 7.5 Hz, NH), 12.21 (1H, s, COOH); ^{13}C NMR (125 MHz, DMSO-d_6, TMS): δ 20.8, 57.7, 110.9, 115.4, 115.6, 120.4, 121.4, 121.7, 128.3, 131.0, 131.1, 132.8, 138.7, 146.5, 172.9, 191.2; found C, 66.39; H, 4.77; N, 8.45%; M + 1 (mass spectrum), 327.3. $C_{19}H_{18}N_2O_3$ requires C, 66.25; H, 4.63; N, 8.58%; M, 326.33.

3-Acyl-1,5-benzodiazepine 5dbb

Yellow solid; 311 mg, 91%; Mp: 190–192 °C; IR (KBr): 3341 (NH), 1693 (C═C), 1629 (C═O), 1534 (C═O) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, TMS): δ 2.18 (3H, s, Me), 5.13 (1H, d, J = 5.0 Hz, CH), 6.24 (1H, d, J = 5.5 Hz, NH), 6.56–6.74 (3H, m, Ph), 7.02 (1H, d, J = 8.5 Hz, CH), 7.46–7.53 (4H, m, Ph), 9.46 (1H, d, J = 8.0 Hz, NH), 12.18 (1H, s, COOH); ^{13}C NMR (125 MHz, DMSO-d_6, TMS): δ 20.8, 57.6, 111.0, 120.5, 121.4, 121.7, 128.2, 128.6, 130.4, 132.9, 134.8, 138.7, 139.6, 146.6, 172.8, 191.1; found C, 63.11; H, 4.49; N, 8.09%; M + 1 (mass spectrum), 343.2. $C_{18}H_{15}ClN_2O_3$ requires C, 63.07; H, 4.41; N, 8.17%; M, 342.78.

3-Acyl-1,5-benzodiazepine 5ebb

Red solid; 335 mg, 95%; Mp: 196–198 °C; IR (KBr): 3349 (NH), 1693 (C═C), 1645 (C═O), 1541 (C═O) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, TMS): δ 2.18 (3H, s, Me), 5.18 (1H, d,

J = 5.0 Hz, CH), 6.30 (1H, d, J = 5.5 Hz, NH), 6.58–6.76 (3H, m, Ph), 6.97 (1H, d, J = 8.5 Hz, CH), 7.68–8.31 (4H, m, Ph), 9.59 (1H, d, J = 8.5 Hz, NH), 12.24 (1H, s, COOH); ^{13}C NMR (125 MHz, DMSO-d_6, TMS): δ 20.8, 57.4, 111.1, 120.7, 121.5, 121.8, 123.9, 128.0, 129.7, 133.2, 138.9, 147.2, 147.3, 148.3, 172.7, 190.1; found C, 61.21; H, 4.37; N, 11.81%; M + 1 (mass spectrum), 354.3. $C_{18}H_{15}N_3O_5$ requires C, 61.19; H, 4.28; N, 11.89%; M, 353.33.

3-Acyl-1,5-benzodiazepine 5fab

Deep yellow solid; 286 mg, 95%; Mp: 118–120 °C; IR (KBr): 3302 (NH), 1684 (C═C), 1629 (C═O), 1534 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6, TMS): δ 5.21 (1H, d, J = 3.5 Hz, CH), 6.42 (1H, d, J = 6.0 Hz, NH), 6.77–6.93 (4H, m, Ph), 8.00–8.03 (2H, m, thiazole ring), 9.19 (1H, d, J = 6.5 Hz, CH), 10.12 (1H, d, J = 8.5 Hz, NH), 12.24 (1H, s, COOH); ^{13}C NMR (125 MHz, DMSO-d_6, TMS): δ 57.9, 109.8, 120.7, 120.8, 121.4, 124.4, 125.6, 130.5, 139.2, 144.2, 148.2, 171.0, 172.7, 177.0; found C, 55.71; H, 3.53; N, 14.10%; M − 1 (mass spectrum), 300.1. $C_{14}H_{11}N_3O_3S$ requires C, 55.80; H, 3.68; N, 13.95%; M, 301.32.

3-Acyl-1,5-benzodiazepine 5gab

Brown solid; 274 mg, 93%; Mp: 200–202 °C; IR (KBr): 3357 (NH), 1701 (C═C), 1629 (C═O), 1581 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6, TMS): δ 5.22 (1H, d, J = 2.0 Hz, CH), 6.35 (1H, d, J = 2.5 Hz, NH), 6.74–7.66 (5H, m, pyridine ring), 7.79 (1H, d, J = 8.0 Hz, CH), 7.91–8.61 (4H, m, Ph), 9.68 (1H, d, J = 8.0 Hz, NH), 12.20 (1H, s, COOH); ^{13}C NMR (125 MHz, DMSO-d_6, TMS): δ 57.6, 110.6, 120.5, 120.6, 121.4, 123.9, 124.0, 125.1, 130.7, 137.7, 139.0, 148.0, 148.2, 158.3, 172.9, 188.7; found C, 65.22; H, 4.61; N, 14.01%; M + 1 (mass spectrum), 295.9. $C_{16}H_{13}N_3O_3$ requires C, 65.08; H, 4.44; N, 14.23%; M, 295.30.

3-Acyl-1,5-benzodiazepine 5fac

Yellow solid; 303 mg, 92%; Mp: 164–166 °C; IR (KBr): 3318 (NH), 1709 (C═C), 1629 (C═O), 1522 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6, TMS): δ 0.94 (3H, t, J = 7.0, Me), 3.90 (2H, q, J = 2.5, CH_2), 5.25 (1H, d, J = 4.5 Hz, CH), 6.53 (1H, d, J = 6.0 Hz, NH), 6.95–8.04 (6H, m, Ph), 8.01–8.04 (2H, m, thiazole ring), 9.23 (1H, d, J = 7.0 Hz, CH), 10.18 (1H, d, J = 8.5 Hz, NH); ^{13}C NMR (125 MHz, DMSO-d_6, TMS): δ 14.5, 57.9, 60.6, 109.1, 120.9, 121.0, 121.3, 124.5, 125.7, 130.8, 138.8, 144.2, 148.4, 170.8, 171.1, 177.0; found C, 58.27; H, 4.41; N, 12.85%; M + 1 (mass spectrum), 330.2. $C_{16}H_{15}N_3O_3S$ requires C, 58.34; H, 4.59; N, 12.76%; M, 329.37.

3-Acyl-1,5-benzodiazepine 5gac

Pale gray solid; 287 mg, 89%; Mp: 164–166 °C; IR (KBr): 3318 (NH), 1717 (C═C), 1645 (C═O), 1526 (C═O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6, TMS): δ 0.96 (3H, t, J = 7.0, Me), 3.91 (2H, q, J = 5.5, CH_2), 5.23 (1H, d, J = 5.5 Hz, CH), 6.44 (1H, d, J = 5.5 Hz, NH), 6.76–7.66 (5H, m, pyridine ring), 7.83 (1H, d, J = 8.5 Hz, CH), 7.92–8.61 (4H, m, Ph), 9.72 (1H, d, J = 8.5 Hz, NH); ^{13}C NMR (125 MHz, DMSO-d_6, TMS): δ 14.6, 57.7, 60.5, 109.9, 120.5, 120.9, 121.3, 123.9, 124.0, 125.1, 131.0, 137.7, 138.6, 148.1, 148.2, 158.1, 171.3, 188.5; found C, 66.79; H, 5.16; N, 13.23%; M + 1 (mass spectrum), 323.9. $C_{18}H_{17}N_3O_3$ requires C, 66.86; H, 5.30; N, 13.00%; M, 323.35.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (21776060 and 21276064) and the Natural Science Foundation of Hebei Province (B2016205165).

Notes and references

1 G. Wess, M. Urmann and B. Sikenberger, *Angew. Chem.*, 2001, **113**, 3443, (*Angew. Chem., Int. Ed.*, 2001, **40**, 3341).
2 G. Grossi, M. Di Braccio, G. Roma, V. Ballabeni, M. Tognolini, F. Calcina and E. Barocelli, *Eur. J. Med. Chem.*, 2002, **37**, 933.
3 A. Maleki and M. Kamalzare, *Catal. Commun.*, 2014, **53**, 67.
4 Y. Y. Shen, J. Han and X. C. Sun, *Tetrahedron*, 2015, **71**, 4053.
5 M. Di Braccio, G. Grossi, G. Roma, L. Vargiu, M. Mura and M. E. Marongiu, *Eur. J. Med. Chem.*, 2001, **36**, 935.
6 R. Kaoua, B. Nedjar-Kolli, T. Roisnel, Y. L. Gal and D. Lorcy, *Tetrahedron*, 2013, **69**, 4636.
7 G. Saini, P. Kumar, G. S. Kumar, A. R. K. Mangadan and M. Kapur, *Org. Lett.*, 2018, **20**, 441.
8 Y. Segawa, T. Maekawa and K. Itami, *Angew. Chem., Int. Ed.*, 2015, **54**, 66.
9 B. Jiang, C. Li, F. Shi, S.-J. Tu, K. Parminder, W. Walter and G. Li, *J. Org. Chem.*, 2010, **75**, 2962.
10 L. Z. Wang, X. Q. Li and Y. S. An, *Org. Biomol. Chem.*, 2015, **13**, 5497.
11 Y. Y. Wu, K. Q. Tian, T. Yang, X. Q. Du and P. Zhang, *Chin. J. Org. Chem.*, 2013, **33**, 1465.
12 Y. J. Jiang, J. J. Cai, J. P. Zou and W. Zhang, *Tetrahedron Lett.*, 2010, **51**, 471.
13 L. Y. Yin and L. Z. Wang, *Tetrahedron Lett.*, 2016, **57**, 5935.
14 C. J. Menet, S. R. Fletcher and G. Van Lommen, *J. Med. Chem.*, 2014, **57**, 9323.
15 A. Z. A. Hassanien, S. A. S. Ghozlan and M. H. Elnagdi, *J. Heterocycl. Chem.*, 2003, **40**, 225.
16 Y. W. Sun and L. Z. Wang, *New J. Chem.*, 2018, **42**, 20032.