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Green synthesis of pyrrole-fused dibenzoxazepine/dibenzothiazepine/-triazolobenzodiazepine derivatives *via* isocyanide-based multicomponent reactions

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Abstract: An efficient and facile synthesis of pyrrole-fused dibenzoxazepine/dibenzothiazepine/ triazolobenzodiazepine derivatives were developed through the isocyanide-based multicomponent reaction of isocyanides, gem-diactivated olefins and cyclic imines such as dibenzoxazepine, dibenzothiazepine and triazolobenzodiazepine under solvent- and catalyst-free conditions. Purposefully, this approach produced various biological scaffolds using environmentally friendly, mild, and simple conditions. Due to their bioactive moieties, these compounds with exclusive fluorescence properties may attract great attention in biomedical applications, clinical diagnostics, and conjugate materials.

Keywords: Isocyanides, Pyrrole, Cyclic imines, Multicomponent reactions, Dibenzoxazepine, Dibenzothiazepine, Triazolobenzodiazepine

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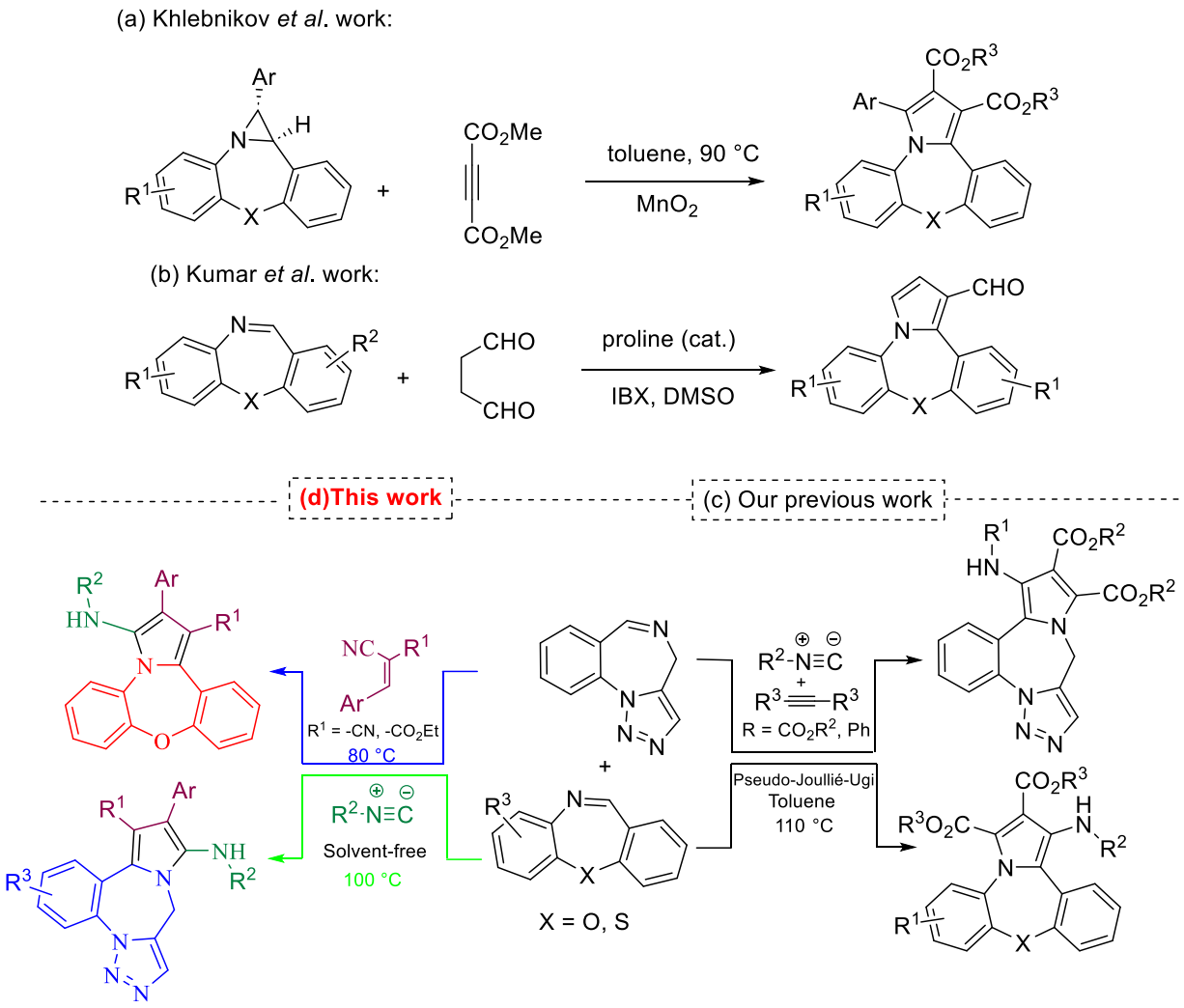
Introduction

Pyrroles and its derivatives are important *N*-heterocyclic compounds with antibiotics, antiviral, and anticancer properties, that exist in many drugs and natural products.[1-6] The biological properties of pyrroles are manifested when they are fused to other heterocycles.[7-12] Especially the seven-membered heterocycles of the benzodiazepine, benzoxazepine, and benzothiazepine derivatives, which include the central core of many natural and biological compounds and commercial drugs, including diazepam, clonazepam, lorazepam, telenzepine, chlordiazepoxide, loxapine, and amoxapine.[13-21] Pyrrole-fused benzodiazepines, benzoxazepines, or benzothiazepines exhibit unique biological and pharmacological properties.[22, 23] For example, Anthramycin, which is used in tumor treatment, or PBOX-6 as a drug for the treatment of depression, is made of pyrrole-fused benzoxazepines.[24] Because of their broad applications, new approaches have been reported for synthesizing pyrrole-fused benzodiazepines, benzoxazepines, and benzothiazepines.[25-29] For example, pyrrole-fused dibenzoxazepines were created *via* a sequential 1,3-dipolar cycloaddition/aromatization reaction in the presence of MnO_2 by Khlebanikov co-workers (Scheme 1a).[30] In another report, pyrrole-fused dibenzoxazepines were synthesized by Kumar *et al*, through [2+3] cyclization between aqueous dibenzoxazepines and succinaldehyde in the presence of proline and IBX as an oxidizing agent and catalyst (Scheme 1b).[31] In our recent studies, we prepared pyrrole-fused triazolobenzodiazepine, benzothiazepine or dibenzoxazepines *via* a pseudo-Joullié-Ugi three-component reaction (Scheme 1c).[32-34]

Here, we report an efficient and facile approach for the synthesis of pyrrole-fused, dibenzoxazepine, dibenzothiazepine and triazolobenzodiazepine derivatives *via* isocyanide-based multicomponent reaction (I-MCRs) of gem-diactivated olefins, isocyanides, and cyclic imines (dibenzoxazepines, benzothiazepine and triazolobenzodiazepine) under solvent- and catalyst-free conditions (Scheme 1c).



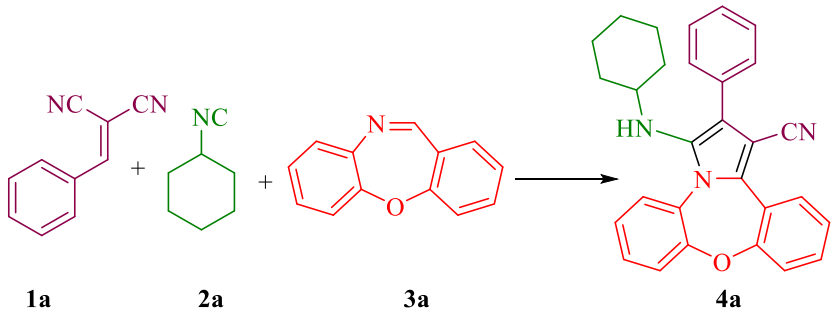
Scheme 1 Methods for the construction of pyrrole-fused seven-membered heterocycles

Results and Discussion

Synthesis

Encouraged by this result, we were able to combine more samples. Before anything, screening the most suitable conditions for this synthesis is necessary. Dibenzoxazepine imine, cyclohexyl isocyanide, and gem-diactivated olefin, (2-benzylidenemalononitrile) were designated as the starting materials to investigate the reaction conditions (Scheme 2, Table 1). First, we investigated the reaction in dichloromethane at room temperature and 40 °C (Table 1, Entries 1, 2). We found that the reaction progresses slightly at 40 °C. According to this promising result, the reaction was examined in multiple anhydrous solvents such as CH_3CN, toluene, EtOH, THF, EtOAc, and DMF under different temperatures (Table 1, Entries 3-9). The result obtained from the study of solvents

showed that pyrrole-fused dibenzoxazepine was obtained with a yield of 56% in ethanol solvent at a temperature of 78 °C (Table 1, Entry 4). To achieve a high yield of product **4a**, an attempt was made to investigate the reaction under solvent-free conditions at different temperatures (Table 1, Entries 10-13). Interestingly, the highest yield of the desired product was achieved by conducting the reaction at 100 °C without using any solvent (Table 1, Entry 12). Also, the reaction was studied under microwave and ultrasonic conditions in dichloromethane, ethanol, and solvent-free at different temperatures, the reaction yield was not improved (Table 1, Entries 14-19).



Scheme 2 The model reaction of dibenzoxazepine imine, gem-diactivated olefin (2-benzylidenemalononitrile), and cyclohexyl isocyanide

Table 1 Optimization of the reaction conditions[a]

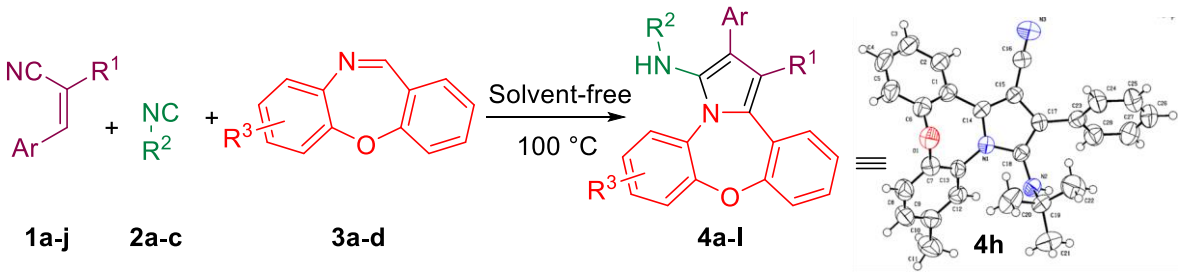
Entry	Solvent	Temperature °C	Time (h)	Yield[b] (%)
1	CH_2Cl_2	25	24	0
2	CH_2Cl_2	40	24	23
3	CH_3CN	82	24	36
4	EtOH	78	24	56
5	Toluene	110	24	33
6	THF	66	24	41
7	H_2O	100	24	Trace
8	EtOAc	77	24	22
9	DMF	140	24	38
10	Solvent-free	25	24	0
11	Solvent-free	80	2	61
12	Solvent-free	100	2	70
13	Solvent-free	120	2	70
14	EtOH	78/MW	0.5	45
15	CH_2Cl_2	40/MW	0.5	Trace
16	Solvent-free	100/MW	0.5	56
17	EtOH	78/US	2	25

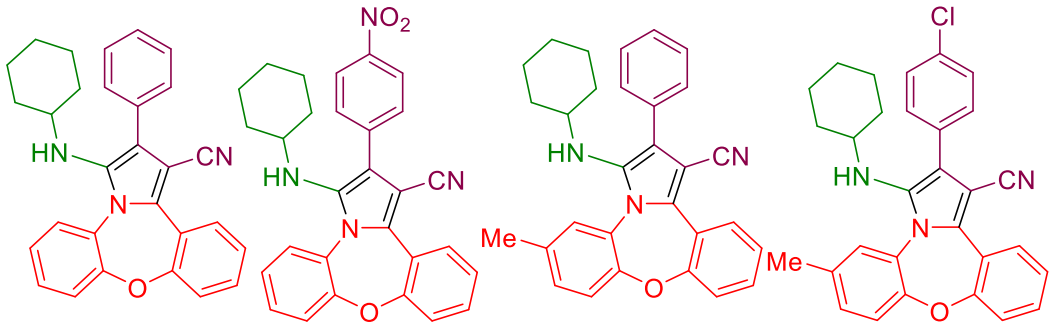
18	CH_2Cl_2	40/US	2	Trace
19	Solvent-free	100/US	2	41

[a] Reaction conditions: **1a** (0.55 mmol), **2a** (0.55 mmol), and **3a** (0.50 mmol) were stirred in 2 mL of solvent in an oil bath at different temperatures and times. [b]Isolated yields.

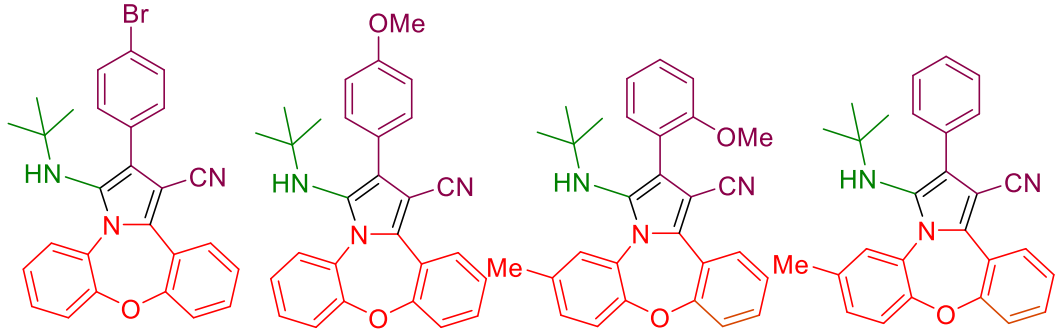
After creating optimal conditions, we studied the scope of this reaction with benzoxazepine, gem-diactivated olefins, and isocyanide derivatives (Scheme 3). As illustrated in Scheme 3, the electron-donating (-Me, -OMe) and electron-withdrawing (-NO_2, Cl, and Br) groups were well tolerated under the optimal reaction conditions. Ultimate products **4** were obtained in yields ranging from 68% to 87% (Scheme 3, **4a**−**4l**). In this reaction, altering the electron-withdrawing and electron-donating effect of the substituents in the aromatic rings of gem-diactivated olefins leads to an increase and a decrease in the yield of the final products **4**, respectively (Scheme 3, **4a**−**4l**). The cause of this phenomenon is probably related to the effect of substitution groups in olefin, which affects the nucleophilic attack of isocyanides. When the carboxylate substituent was substituted for the carbonitrile in the gem-diactivated olefins, the desired products were obtained in good yield (Scheme 3, **4k**−**l**). On the other hand, electron-donating and electron-withdrawing substitutions in dibenzoxazepine imine were investigated in this protocol, in which the substitute of the electron-withdrawing led to an increase and the substitute of the electron-donating led to a decrease in the reaction efficiency (Scheme 3, **4a**−**4k**). In addition, benzothiazepine imine was used in this protocol and pyrrole-fused benzothiazepine was obtained with a yield of 73% (Scheme 3, **4l**). Also, various isocyanides were suitable for this reaction. By substituting cyclohexyl-, *tert*-butyl-, and isopropyl isocyanide, the yield of pyrrole product was obtained without much difference.

Scheme 3 Substrate scope[a]

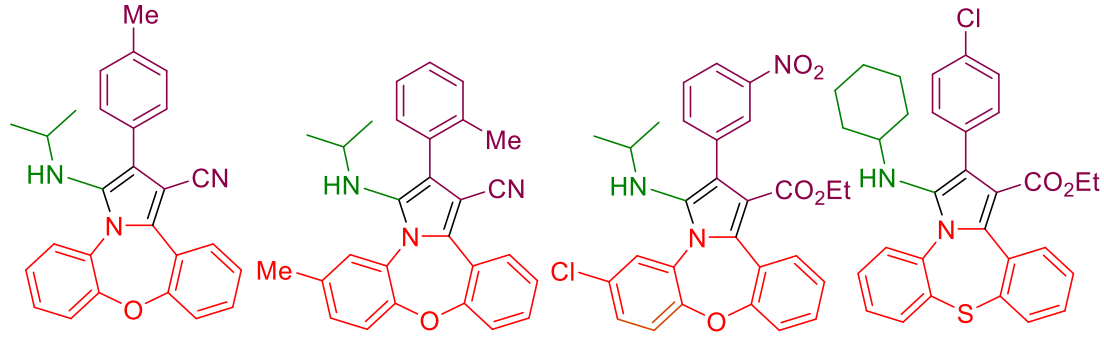




4a, 75% **4b**, 87% **4c**, 71% 4**d**, 79%



4e, 85% **4f**, 73% **4g**, 71% **4h**, 72%

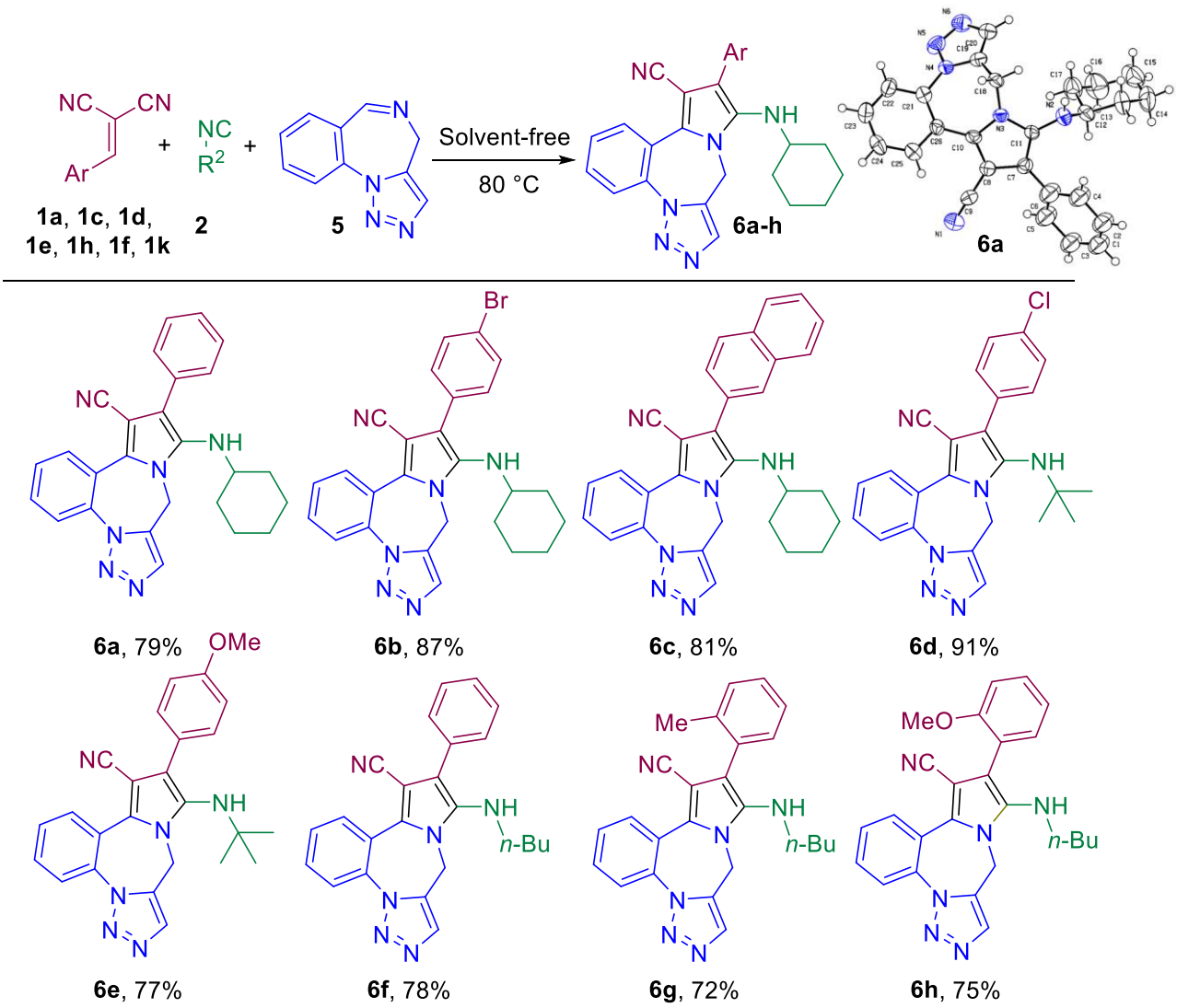


4i, 70% **4j**, 68% **4k**, 82% **4l**, 73%

[a]Reactions were carried out using **1** (0.55 mmol), **2** (0.55 mmol), and **3** (0.50 mmol) under solvent-free conditions, stirring in an oil bath at 100 °C for 2 h (monitored by TLC).

To investigate the reactivity of other cyclic imines in this protocol, triazolobenzodiazepine imine, gem-diactivated olefins, and isocyanides were investigated to synthesize heterocyclic compounds (Scheme 4). As predicted, under almost the same conditions as Scheme 3 (only at 80 °C), a new type of heterocyclic compound, pyrrole-fused triazolobenzodiazepines, was obtained in high yield. As summarized in Scheme 4, a variety of gem-diactivated olefins with electron-donating (-Me, -OMe), electron-withdrawing (-NO_2) and halogens (-Cl and -Br) substitutions on the aromatic ring were well tolerated under optimal reaction conditions. Pyrrole-fused triazolobenzodiazepines **6** were obtained in yields ranging from 72% to 91% (Scheme 4, **6a-h**). Similar to the reaction of benzoxazepine, the effect of the electron-withdrawing group leads to an increase in the yield of pyrrole-fused triazolobenzodiazepines, and the electron-donating group leads to a decrease in its yield. Also, the substitution of naphthyl used in gem-diactivated olefins increased the efficiency of the desired product compared to the substitution of phenyl (Scheme 4, **6c**). Furthermore, *n*-butyl isocyanide was used to increase the variety of products and the efficiency of the proposed method in this protocol for synthesizing pyrrole-fused to triazolobenzodiazepine, and products **6** were obtained with 72-78% yield (Scheme 4, **6f-h**).

Scheme 4 Substrate scope[a]



[a]Reactions were carried out using **1** (0.55 mmol), **2** (0.55 mmol), and **5** (0.50 mmol) under solvent-free conditions, stirring in an oil bath at 80 °C for 2 h (monitored by TLC).

All the products were characterized by ^{1}H NMR, and ^{13}C NMR spectroscopy, IR, and Mass. Taking **4h** as an example for the analysis of its structure, in its ^{1}H NMR, one singlet signal appears at δ = 0.67 (9 H) due to the *tert*-butyl groups. A singlet at δ = 2.39 (3 H) is the proton of CH_3 on phenyl. The signal at δ = 3.42 is the NH group. All the protons of the aromatic ring are located from δ = 7.10 to 7.99. In its ^{13}C NMR, all of the carbon signals appear at δ = 158.3, 152.5, 134.7, 134.2, 133.9, 133.2, 130.8, 130.4, 129.2, 129.1, 129.0 128.9, 128.4, 127.4, 125.8, 122.6, 121.1, 120.6, 117.1 (C_{Ar}), 91.1 (CN), 56.8, 29.4, 20.9 ($C_{Aliphatic}$) respectively. In its Mass, the calculated and found values of m/z for $C_{28}H_{25}N_3O$ $[M^+]^+$ is 419. In IR, the absorption peak index in 2213 is

related to the CN group. For final confirmation, the derivative **4h** was studied by X-ray diffraction analysis, and the crystal structure is illustrated in Figure 1 (Detailed information can be found in the SI).

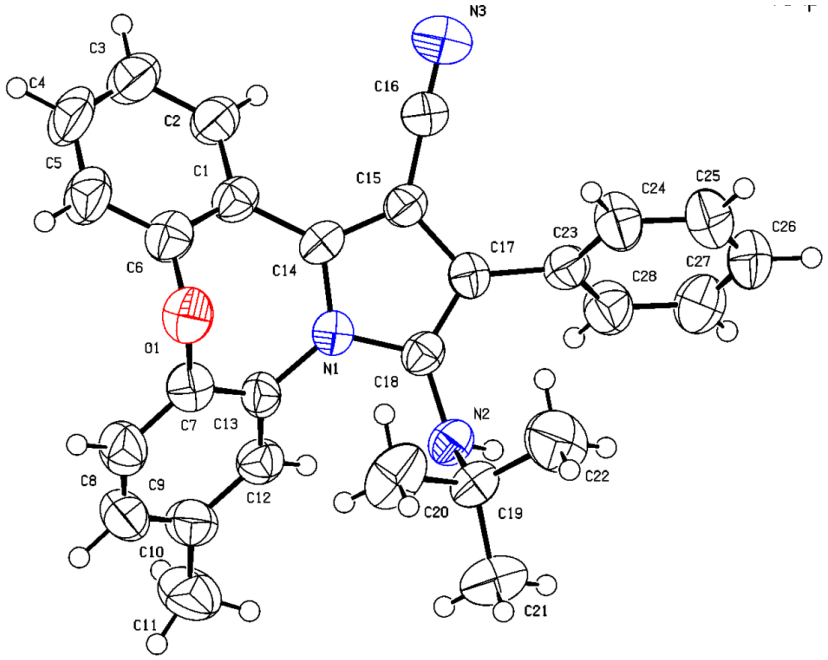


Figure 1 The crystal structure of **4h** (CCDC 2365305)

In **6a** ^{1}H NMR, three multiplet signals at δ = 1.08–0.89 (6 H), and 1.54–1.65 (4 H) should be cyclohexyl protons. A broad singlet signal at δ = 2.56 due to an NC*H* signal could be found. The one (NH) groups are located at δ = 3.49. Two singlet signals appear at δ = 4.63 (1 H), and 5.92 (1 H) due to the CH_2 groups. The one aromatic proton appeared from δ = 7.76 due to the triazole proton. The 9 aromatic protons appeared from δ = 7.28 to 8.17. In the ^{13}C NMR, all the carbon signals appear at δ = 137.1, 134.4, 134.1, 132.6, 132.2, 131.4, 130.2, 130.2, 129.7, 128.9, 128.5, 124.4, 121.5, 120.6, 116.6, 115.3 (C_{Ar}), 91.8 (CN), 60.4, 53.8, 35.3, 31.8, 29.3, 21.1, 14.2 ($C_{Aliphatic}$), respectively. In its Mass, the calculated and found values of m/z for $C_{26}H_{24}N_6$ $[M^+]^+$ is 420. In IR, the absorption peak index in 2213 is related to the CN group. For final confirmation, the derivative **6a** was studied by X-ray diffraction analysis, and the crystal structure is illustrated in Figure 2 (Detailed information can be found in the SI).

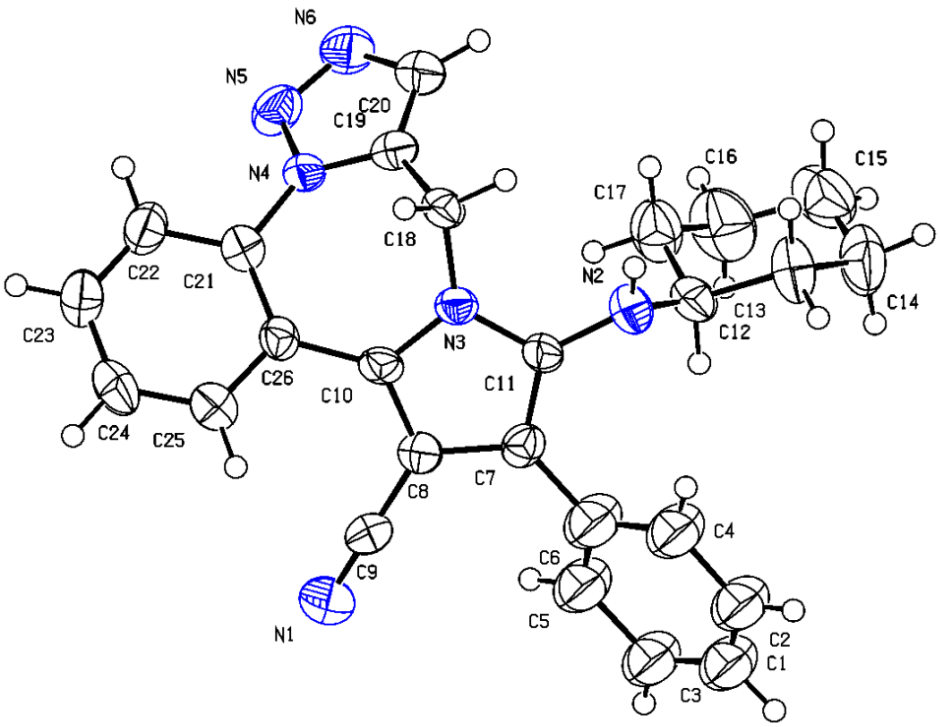


Figure 2 The crystal structure of **6a** (CCDC2365306)

^{1}H NMR of product **6f** obtained through the I-MCRs was investigated and all unexpected chemical shifts in product **6f** were observed at room temperature (Figure 3A).[35] Dynamic NMR was prepared from compound 6f at various temperatures 25, 35, 45, 55, 65, 75, and 85 °C to prove this assertion. As illustrated in Figure 3, spectrum **A** has two broad singular peaks at δ = 4.65 and δ = 5.84 corresponding to hydrogen **I** and hydrogen **II**. Remarkably, at higher temperatures (85 °C), the rapid inversion of the seven-membered ring results in it being observed as a single structure on the ^{1}H NMR time scale (see Figure 3, **F** spectrum).[19, 36, 37]

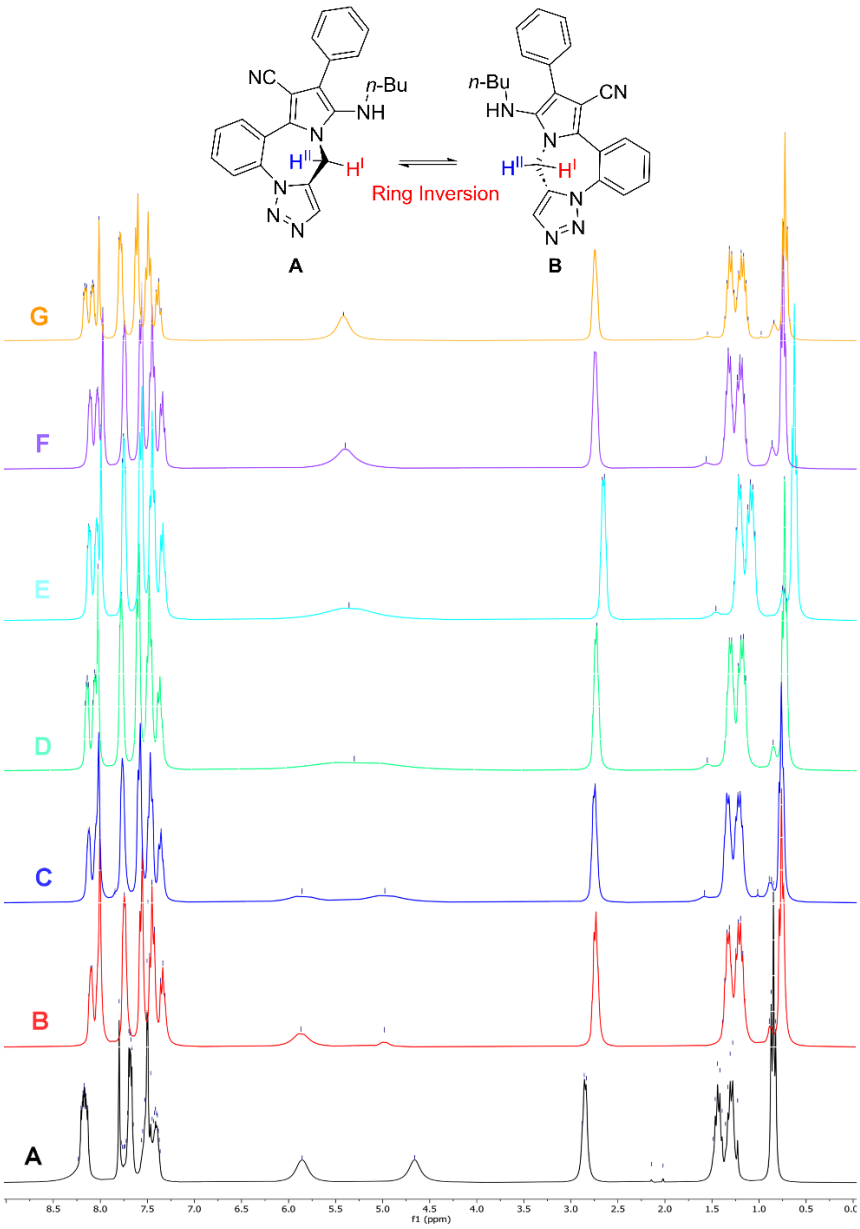
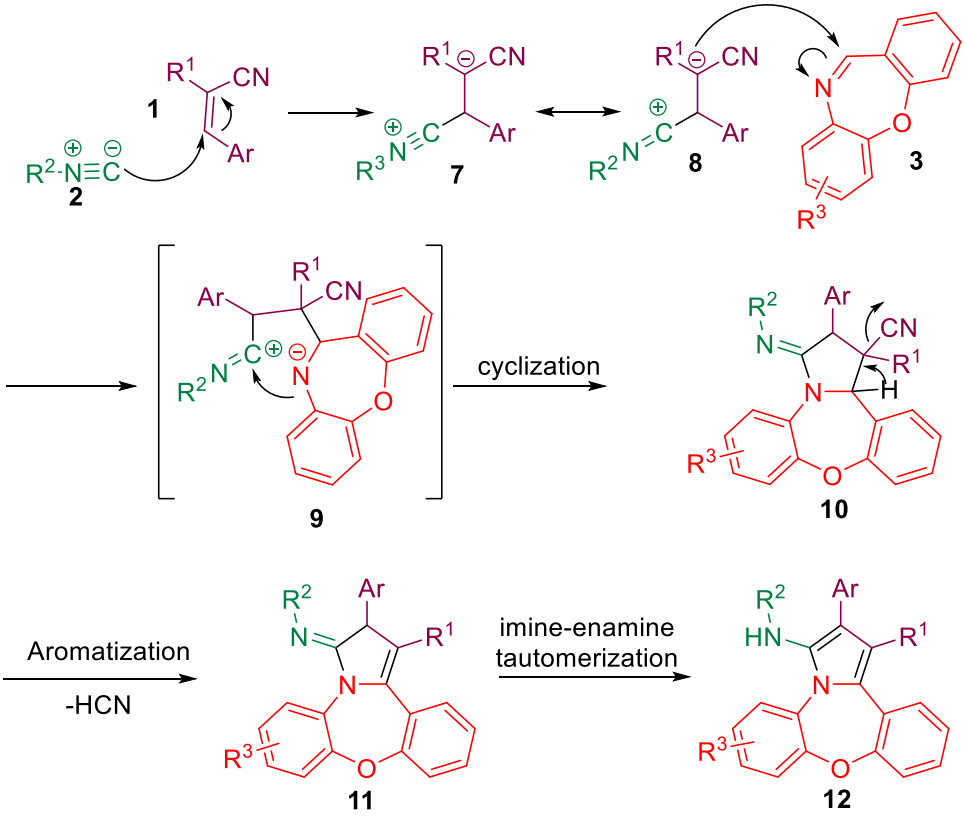


Figure 3 The DNMR (Dynamic Nuclear Magnetic Resonance) spectra of compound **6f** (DMSO-d_6, 300 MHz) at 25-85 °C; spectrum A: 25 °C, spectrum B: 35 °C, spectrum C: 45 °C, spectrum D: 55 °C, spectrum E: 65 °C, spectrum F: 75 °C and spectrum E: 85 °C

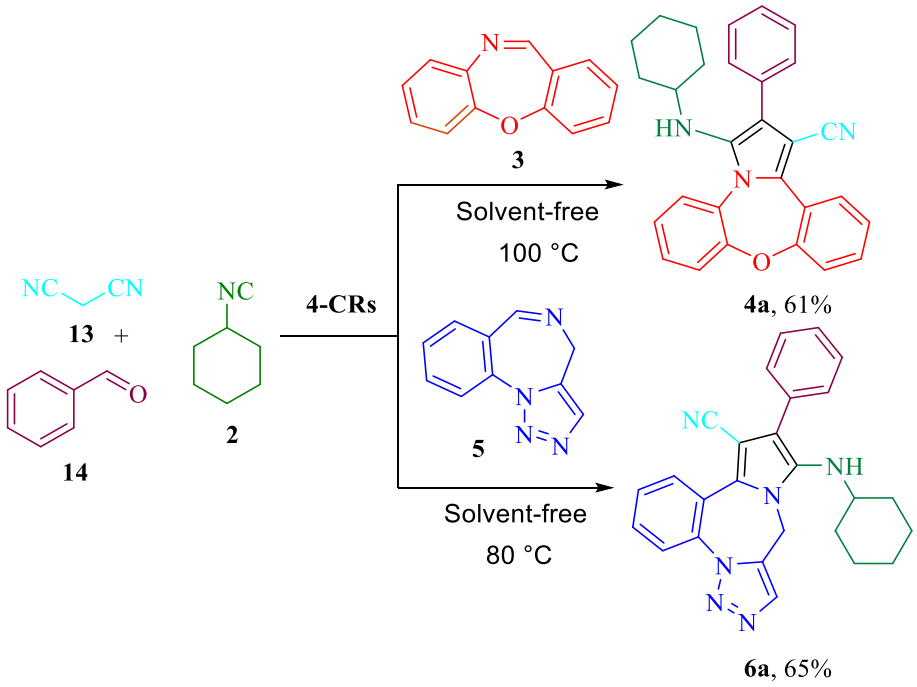
Based on the experimental facts described above, the proposed mechanism for this multicomponent domino reaction was presented in Scheme 5: First, an isocyanide **2** is added to the gem-diactivated olefins-passivated olefin **1**. The reaction proceeds with the nucleophilic attack of the resulting zwitterion intermediate **7** on the cyclic imine. Then, with the cyclization process,

the intermediate **10** is obtained. Finally, pyrrole-fused benzoxazepine was obtained by aromatization and tautomeric enamine imine with loss of HCN.



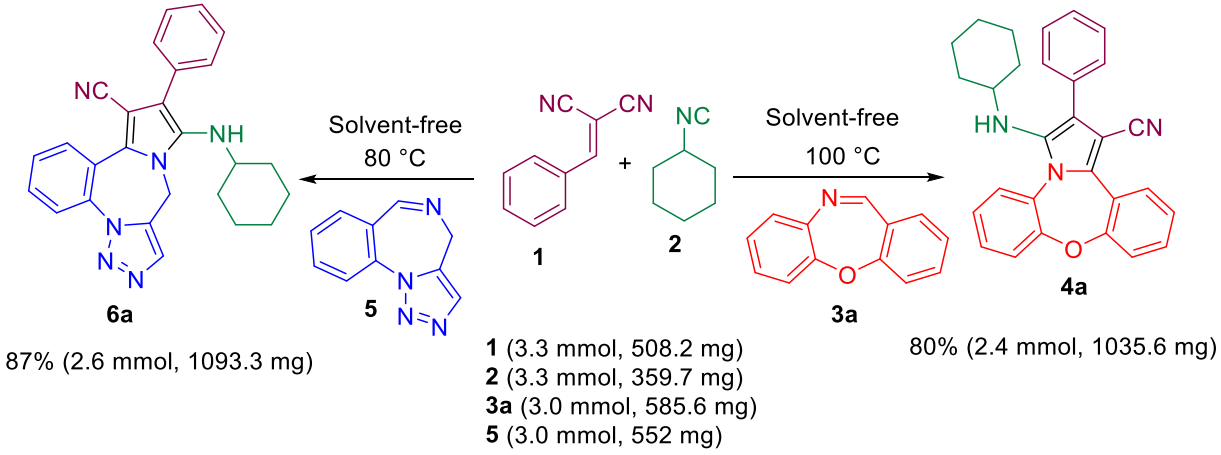
Scheme 5 A suggested mechanism of compounds **4** and **6**

The successful synthesis of pyrrole-fused benzoxazepine/triazolobenzodiazepine derivatives *via* a three-component reaction (3-CR) prompted us to investigate the synthesis of these compounds as a four-component reaction (4-CR). Fortunately, pyrrole-fused benzoxazepine/triazolobenzodiazepine **4a** and **6a** were also synthesized through a one-pot 4-CR from benzaldehyde, malononitrile, cyclohexyl isocyanide, and benzoxazepine/triazolobenzodiazepine imine (Scheme 6). The yield of these products based on the four-component method was lower compared to the three-component strategy.



Scheme 6 Synthesizing of pyrrole-fused dibenzoxazepine/triazolobenzodiazepine through a 4-CR

After efficiently and simply synthesizing pyrrole-fused dibenzoxazepine/triazolobenzodiazepine derivatives on a submillimolar scale, two reactions were conducted on a gram scale to validate the protocol's efficacy (Scheme 7). Each of the cyclic imines in the amount of 1.5 mmol for synthesizing pyrrole-fused dibenzoxazepine/triazolobenzodiazepine **4a** and **6a** were obtained with 80 and 87% yields, respectively. In general, a significant increase in the yield of products was observed compared to the millimole state.



Scheme 7 Gram-scale synthesis of pyrrole-fused dibenzoxazepine/triazolobenzodiazepine **4a** and **6a** *via* 3-CRs

Physical properties

The compounds such as benzoxazepines, benzothiazepines, benzodiazepines, and pyrrole have shown promising applications in optoelectronics, biophotonics, and cell imaging due to their suitable fluorophores.[38-40] The UV-vis absorption and emission spectra of products **4** and **6** were studied in ethanol at 298 K. The absorption range (λ_{abs}) was 400-225 nm, and the emission range (λ_{emi}) was 560-400 nm. These findings are shown in Figure 3S in the Supporting Information. An interesting trend for the absorption of the synthesized derivatives **4** and **6** was observed when electron-donating substituents were substituted in the phenyl ring, which led to an increase in the intensity of the absorption and emission wavelengths (Supporting Information Figure 3S). As is evident in numerous reports, quantum yield is one of the most important photophysical parameters for describing luminescent molecules and materials since high quantum efficiency is important for a wide range of applications, including displays, lasers, bio-imaging, solar cells, and accurate measurement of the quantum yield is therefore important.[41-43] Therefore, the quantum yield was determined using the standard of quinone sulfate for all the products (**4a-l** and **6a-h**). Products **4a** and **6c**, which had the highest intensity of absorption and emission from derivatives of benzoxazepines and triazolobenzodiazepines, respectively, their quantum yield was calculated and **4a** was obtained with 48.35% and **6c** with 1.04% (Figure 4A and 4B).[44] According to the results obtained from the quantum yield, we can claim that these synthesized derivatives pyrrole-fused dibenzoxazepine/dibenzothiazepine/triazolobenzodiazepine derivatives serve as potential candidates for optoelectronic conjugate materials.[45]

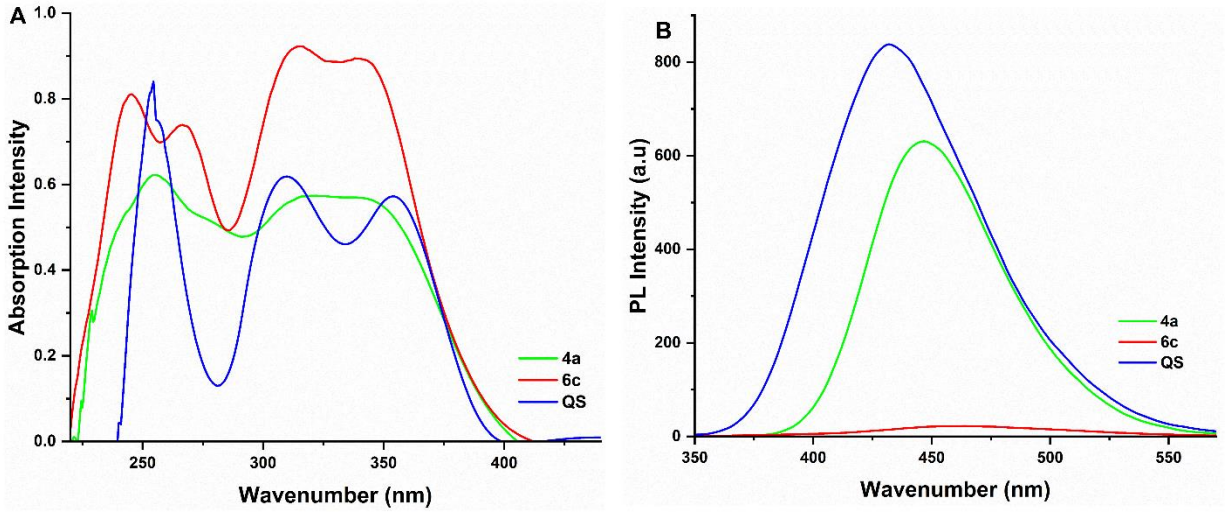


Figure 4 UV-Vis absorption for compounds **4a**, **6c** and **QS** (Quinine Sulfate) (a); emission for **4a**, **6c** and **QS** (b); c = 75 ppm in ethanol and T = 298 K.

Conclusion

In summary, we have designed a simple and novel procedure for synthesizing pyrrole-fused dibenzoxazepine/dibenzothiazepine/triazolobenzodiazepine derivatives in high yields. This one-pot 3-CR includes isocyanides, gem-diactivated olefins, and cyclic imines (dibenzoxazepines, dibenzothiazepine, and triazolobenzodiazepine) under catalyst- and solvent-free conditions. Furthermore, the other advantages of this reaction include the production of manufacturing premium pharmaceutical scaffolds, a wide range of substrates, short reaction times, simple operation, and green conditions. According to the quantum efficiency calculation, all pyrrole-fused dibenzoxazepine/dibenzothiazepine/triazolobenzodiazepine derivatives with excellent emission can serve as potential candidates for optoelectronic conjugate materials.

Experimental

General information

All commercially available reagents and chemicals were bought from Merck & Co. and utilized without extra purification. The melting points of all the synthesized were measured utilizing an Electrothermal 9200 apparatus. ^{1}H and ^{13}C NMR and spectra in $CDCl_3$ and DMSO-d_6 solvents were recorded on a BRUKER AVANCE spectrometer at 300.13 MHz and 75.47 MHz, respectively. IR spectra were created on a Thermo Nicolet NEXUS 470 FT-IR spectrometer in cm^{-}

[1]. Mass spectra with an HP (Agile Technologies) 5975C Mass Selective Detector were used to confirm the mass of the synthesized products. The PL spectra prepared for the products were obtained by a spectrofluorometric (LS45, PerkinElmer). Elemental analyses were conducted using the GmbH VarioEL CHN mode elementaranalyse system. The ultrasound used for the reactions was carried out in a Specord S 600 ultrasound cleaner device with a frequency of 45 kHz and an output power of 350 W.

Preventive Education for Synthesizing Triazolobenzodiazepine 6a-h.

Azides are highly reactive, toxic, explosive, and shock-sensitive chemicals that can be used under certain conditions. Special safety procedures must be followed during preparation, storage, handling, and disposal. $TMSN_3$ is an organic azide that is very sensitive to external factors such as light, heat, friction, and pressure. Which should be stored in amber plastic containers without light and at a temperature below zero degrees Celsius. Exposure to azide occurs through skin absorption, inhalation, or ingestion through the respiratory tract. Which leads to skin and eye irritation, blurred vision, dizziness, weakness/fatigue, hypotension, seizures, and respiratory failure. The following instructions are required to work with $TMSN_3$. It is necessary to have a silver shield apron, breathing mask, safety glasses, lab coat, and gloves with high chemical resistance. The reaction should be carried out in a hood with a strong suction and with a protective explosion shield, which in this test should be as low as possible. Since exposure to water and strong acids leads to the formation of hydrazoic acid, which is very toxic, volatile, and explosive, therefore, the reaction containers must be completely dry and clean. When consuming $TMSN_3$, it should be done cold (below zero degrees Celsius) in a container insulated from light. The reaction must be completely closed under the hood and the lid of the reaction container, and the product purification process must be carried out under the mentioned personal protective equipment. The reaction on a larger scale is carried out under special safety conditions.[46-48]

3-(Cyclohexylamino)-2-phenyldibenzo[*b,f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbonitrile (4a); Ethyl 2-(4-chlorophenyl)-3-(cyclohexylamino)dibenzo[*b,f*]pyrrolo[1,2-*d*][1,4]thiazepine-1-carboxylate (4e) and 11-(Cyclohexylamino)-12-phenyl-9*H*-benzo[*f*]pyrrolo[1,2-*d*][1,2,3]triazolo[1,5-*a*][1,4]diazepine-13-carbonitrile (6a); Typical Procedure

Cyclic imines of dibenzo[*b,f*][1,4]oxazepine **3a-c**, dibenzo[*b,f*][1,4]thiazepine **3d** and 4*H*-benzo[*f*][1,2,3]triazolo[1,5-*a*][1,4]diazepine **5** were prepared according to the procedure in the previous report[32, 33] and 0.50 mmol (**3a**, 98 mg; **3d**, 105 mg; **5**, 92 mg) of each was added separately along with 2-benzylidenemalononitrile **1a** (0.55 mmol, 85 mg), cyclohexyl isocyanide **2a** (0.55 mmol, 60 mg). The reaction mixture was stirred at temperatures of 100 or 80 °C for 2 h using a magnetic stirrer. After making sure that the reactions were completed (monitored by TLC), the reaction mixture was cooled to ambient temperature. Then, the crudes mixture was purified using a silica gel chromatography column and washed with *n*-hexane and ethyl acetate solvents (1:3 in 3a and 3d; 2:1 in the compounds **5**).

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information Statement

The Supporting Information is available free of charge on the……

^{1}H NMR, ^{13}C NMR FT-IR and Mass spectra (PDF)

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