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Convenient synthesis of substituted benzo[*e*][1,2,4]- or [*d*][1,2,6]oxadiazepines, benzo[*f*][1,3,5]triazocines from *N*-aryliminoesters

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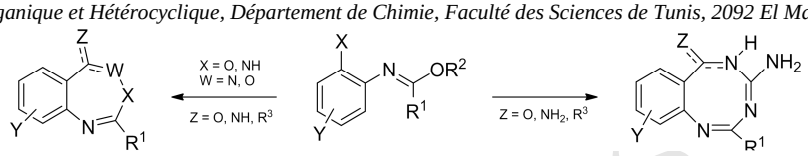

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Convenient Synthesis of Substituted Benz[*e*][1,2,4]- or [*d*][1,2,6]oxadiazepines, Benzo[*f*][1,3,5]triazocines from *N*-Aryliminoesters

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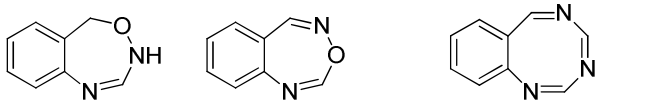
ABSTRACT

We report herein a short and efficient synthesis of benz[*e*][1,2,4]- or [*d*][1,2,6]oxadiazepines and benzo[*f*][1,3,5]triazocines from easily prepared *N*-aryl iminoesters. The strategy involves a bis-nucleophile reagent (hydroxylamine or guanidine) that promotes a one-step ring closure from the starting functionalized iminoesters.

1. Introduction

Considering chemical reactivity as well as potential biological activity, condensed heterocycles containing more than one heteroatom appear to be attractive targets in organic chemistry. Because the development of convenient synthesis of such species remains an exciting challenge, we focused our attention on the synthesis of benzoxadiazepine and benzotriazocine scaffolds. Benzoxadiazepines and benzotriazocines are condensed heterocycles resulting from combination of benzene ring and, respectively, a 7-membered heterocycle bearing one oxygen and two nitrogen atoms or an 8-membered heterocycle bearing three nitrogen atoms.

Although some articles and patents describe benzoxadiazepines and their activities as stimulant to the central nervous system,[1] muscle relaxant,[2] tranquilizer, anti-bacterial, anti-inflammatory[3] or pesticides,[4] the synthesis of these heterocycles has been scarcely investigated in the literature. Benzoxadiazepines are reported as intermediates in the synthesis of quinazolines,[5] benzoxadiazepines,[6] or benzimidazoles.[7] More recently, several oxadiazepine ring closure procedures have been reported involving diazonium coupling reactions as key-step,[8] as well as cyclocondensation[9] or Pd-catalyzed *N*-arylation of amidoximes.[10] Similarly, for benzotriazocines, only few patents have reported their potential biological activities[11] as analgesic and sedative or psychotropic agents. Probably due to their complex and sensitive structure, syntheses of benzotriazocines have not been particularly studied and a limited number of synthetic strategies are reported in the literature. To the best of our knowledge, the first published synthetic pathways of those 8-membered condensed heterocycles have been reported more than forty years ago. The most widely reported sequence leads to the synthesis of benzotriazocine moiety by using addition reaction of hydrazines or amines as nucleophiles with carbonyls and analogs, nitrile, ester or amide aryl derivatives,[12] or, as described more recently, imidoyl chloride and analogs.[13] One example of nucleophilic attack of hydrazone with chloroacetamido aryl derivatives has been reported too.[14] On the other hand, [1,4,5]-benzotriazocines are obtained by treatment of quinazoline *N*-oxide with hydrazine,[15] while the [1,3,4]-isomer can be synthesized using hetero Diels Alder cycloaddition starting from benzazetes with tetrazides, followed by spontaneous extrusion of nitrogen.[16] In light of this review, we have considered that the development of new efficient and short synthetic pathways to such heterocycles remains a major challenge to enable their study. So, among the different isomers of benzoxadiazepine core, the benzo[*e*][1,2,4]- and [*d*][1,2,6]-isomers as well as benzo[*f*][1,3,5]triazocines were chosen as targets of our research (figure 1). We report herein a short and convenient access to the entitled structures using aryliminoester as precursor.



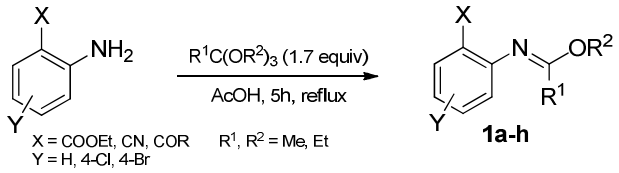
Benz[*e*][1,2,4]- or [*d*][1,2,6]oxadiazepines Benzo[*f*][1,3,5]triazocines

Figure 1. Expected 7- or 8-membered heterocycles.

2. Results and discussion

Iminoesters, as promising intermediates for the synthesis of polycondensed heterocycles, were easily prepared by condensation of substituted aryl amines, using an excess of the appropriate orthoester (1.7 equiv), in the presence of acetic acid as catalyst. Expected derivatives were obtained in good to excellent yields (table 1, 81-96%).

Table 1. Synthesis of iminoesters **1a-h**.



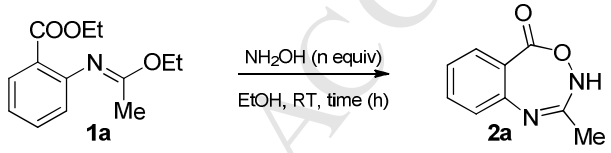
	X	Y	R^1	R^2	Yields (%)[a]
1a	COOEt	H	Me	Et	**84**
1b	COOEt	H	Et	Me	**92**
1c	CN	H	Me	Et	**85**
1d	CN	H	Et	Me	**89**
1e	COPh	4-Cl	Et	Me	**93**
1f	$COCH_3$	H	Me	Et	**96**
1g	$COCH_3$	H	Et	Me	**94**
1h	COOMe	4-Br	Et	Me	**81**

[a] Isolated yield after purification by reduced pressure distillation (0.1 mmHg).

Since substrates **1a-h** exhibit two electrophilic active sites (ester, nitrile or ketone and iminoester respectively), a one-pot ring closure strategy was implemented using bis-nucleophile reagents to prepare the desired condensed heterocycles.

At first, the preparation of benz[*e*][1,2,4]oxadiazepine ring **2a** was studied, requiring hydroxylamine as bis-nucleophile reagent (table 2). Indeed, the choice of this reagent was directly related to our aim to prepare the entitled 7-membered condensed cyclic system from iminoester as starting material. Given the relative positions of the two electrophilic centers on the substrate (imino ester and ester or nitrile or carbonyl), the selected reagent has to possess a nitrogen and an oxygen nucleophilic sites in adjacent position, therefore hydroxylamine seems to be an unavoidable choice.

Table 2. Screening of reaction conditions for preparation of 2-methylbenz[*e*][1,2,4]oxadiazepin-5(3*H*)-one (**2a**).

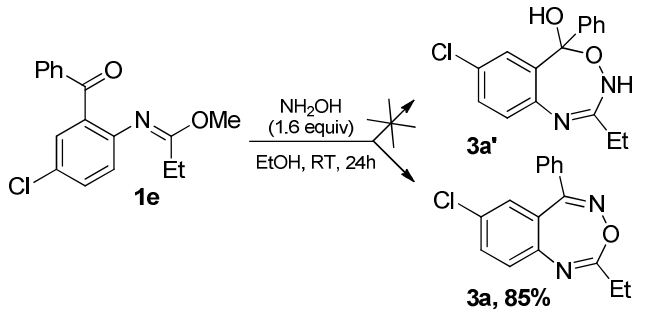


entry	NH_2OH (n equiv)	Time (h)	Yields (%)[a]
1	1.0	12	**17**
2	1.6	12	**21**
3	**1.6**	**24**	**58**
4	1.6	72	**59**
5	2.0	24	**52**
6	2.0	72	**54**

[a] Isolated yield after purification by precipitation and successive washes in Et_2O.

Reaction using only 1.0 equivalent of hydroxylamine in ethanol (EtOH) as solvent for 12 h at room temperature yielded a poor amount of expected heterocycle **2a** (entry 1, 17%). While similar results were obtained by using an excess of hydroxylamine for a reaction time of 12 h at room temperature (entry 2, 1.6 equiv, 21%), a significant increase was observed after stirring at room temperature for 24 h (entry 3, 58%). However, a longer reaction time (entry 4, 72 h, 59%) or the use of 2 equivalents of hydroxylamine (entries 5 and 6, 52 and 54% respectively) did not significantly improve the yield.

Therefore, we decided to use the optimized conditions (see table 2, entry 3) to extend the scope of the procedure to the synthesis of various benz[*e*][1,2,4]oxadiazepin-5(3*H*)-ones (**2a-c**). As shown in table 3, the expected 7-membered heterocycles **2a-c** were obtained in good yields (58, 61 and 74% yield respectively). It should be stated here that the reaction sequence easily tolerates the presence of a bromine atom on the aromatic ring (**2c**). Thereafter, with the aim to synthesize heterocyclic-imine analogs, the same reaction conditions were applied from cyanophenyl iminoesters **1c-d** as starting material. After 24 h in the presence of hydroxylamine (1.6 equiv) in EtOH at room temperature, the expected benz[*e*][1,2,4]oxadiazepin-5(3*H*)-imines **2d-e** have also been obtained in good yields (61 and 79% respectively). Based on these first results, we decided to extend the scope of the sequence to benzoyl- or acetylphenyl iminoesters **1e-g** containing a carbonyl group as second electrophilic unit. Unfortunately, treatment of benzoyliminoester **1e** by hydroxylamine did not afford the anticipated product **3a'**. Instead, as revealed by mass spectroscopy and NMR analyses, a dehydration step that cannot be planned from **3a'**occurred during leading to the formation of compound **3a**. A new mechanism pathway allowed us to propose a structure for **3a** (Scheme 1). More specifically, from **1a-d** and **1h**, benzoxadiazepine ring closure involves an *N*-nucleophilic addition of hydroxylamine on the iminoester substituent that exhibits a higher reactivity compared to the ester or nitrile groups. Consequently, a N=C-N link is formed in the intermediate compound. Then residual hydroxyl function reacts with the ester or nitrile moiety leading to expected heterocycle **2a-e**.

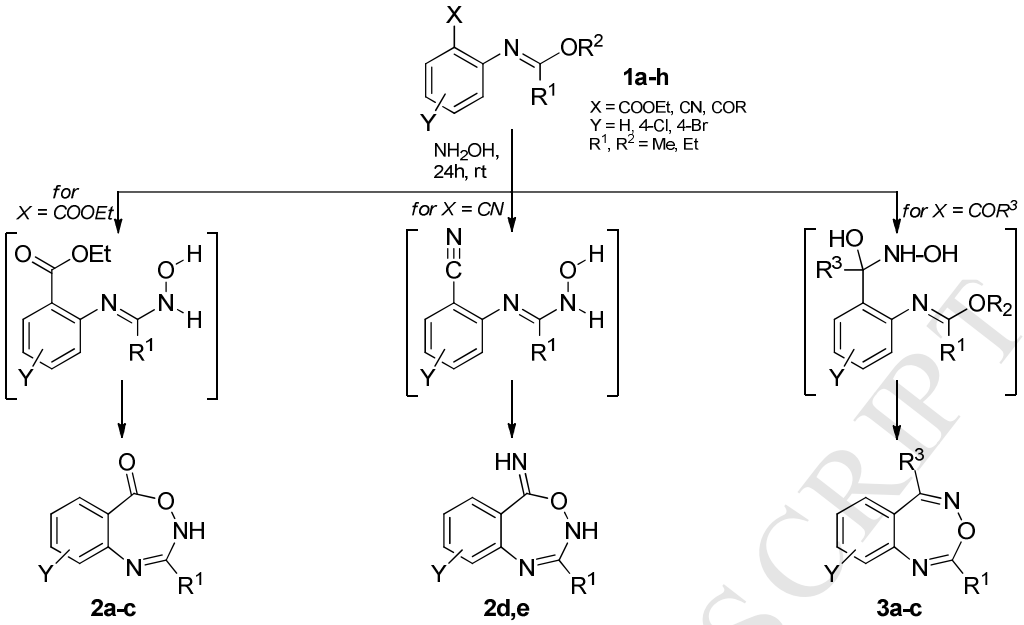


Scheme 1. Formation of benz[*e*][1,2,6]oxadiazepine **3a** *versus* benz[*e*][1,2,4]oxadiazepine **3a'**.

Conversely, concerning carbonyl-iminoester **1e**, the carbonyl group appears to be more electrophilic than the iminoester. Consequently, the *N*-condensation of hydroxylamine occurs first on the carbonyl group. Then, the residual hydroxyl nucleophile reacts with the iminoester group to afford [1,2,6]-isomer **3a** in very good yield (85%) (table 3). These results show that the nature of the second electrophilic site is essential to control the chemo-selectivity of cyclocondensation, to subsequently afford the desired heterocyclic isomers.

Two additional examples were carried out from **1f** and **1g** as substrates affording benz[*e*][1,2,6]-oxadiazepines **3b-c** in good yields (73 and 79% respectively).

Table 3. Preparation of benzoxadiazepines **2a-e** and **3a-c.**



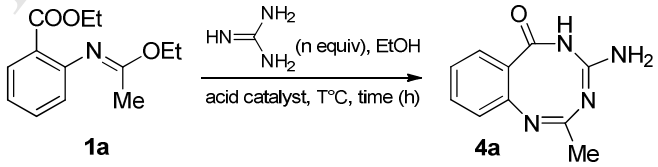
	Y	R^1	Yield (%)[a]		Y	R^1	Yield (%)[a]		R^1	R^3	Y	Yields (%)[a]
2a	H	Me	**58**	**2d**	H	Me	**61**	**3a**	Et	Ph	7-Cl	**85**
2b	H	Et	**61**	**2e**	H	Et	**79**	**3b**	Me	Me	H	**73**
2c	7-Br	Et	**74**					**3c**	Et	Me	H	**79**

[a] Isolated yield after purification by precipitation and successive washes in Et_2O.

Next, we focused our attention on the preparation of the 8-membered heterocyclic benzotriazocine scaffold. Because the target structure was the [1,3,5]-isomer, guanidine ($HN=C(NH_2)_2$) was selected as bis-nucleophile to allow the desired N=C-N=C-N link formation.

As reported in table 4, optimization of reaction conditions was performed. When only one equivalent of guanidine was used in EtOH as solvent for 12 h at room temperature, no transformation was observed and the starting iminoester **1a** was recovered unchanged (entry 1). Furthermore, when increased amount of guanidine (1.6 equiv) was involved, no trace of expected benzotriazocine **4a** was detected, regardless of the reaction temperature (RT or 79 °C). Starting material was recovered once again (entries 2 and 3). To activate the nucleophilic attack on aryliminoester **1a**, an acid catalyst was added to the reaction medium (HCOOH, APTS or AcOH). While no interesting result was observed in the presence of formic acid or APTS (entries 4-7, degradation of substrate or no conversion were observed), the reaction conditions using acetic acid as catalyst, for 24 h and with 1.6 equivalent of reagent led to target heterocycle **4a** in 6% yield for reaction performed at room temperature and 39% yield at 79°C (entries 8 and 9). Finally, a significant increase in yield was observed (63%, entry 10) when a larger excess of guanidine was used (2.0 equivalent). However, it should be noted that an increased reaction time (entry 11, 48h) led to degradation of product **4a** and, consequently, to a decreased yield.

Table 4. Screening of reaction conditions for preparation of 4-amino-2-methylbenzo[*f*][1,3,5]triazocin-6(5*H*)-one (**4a**).



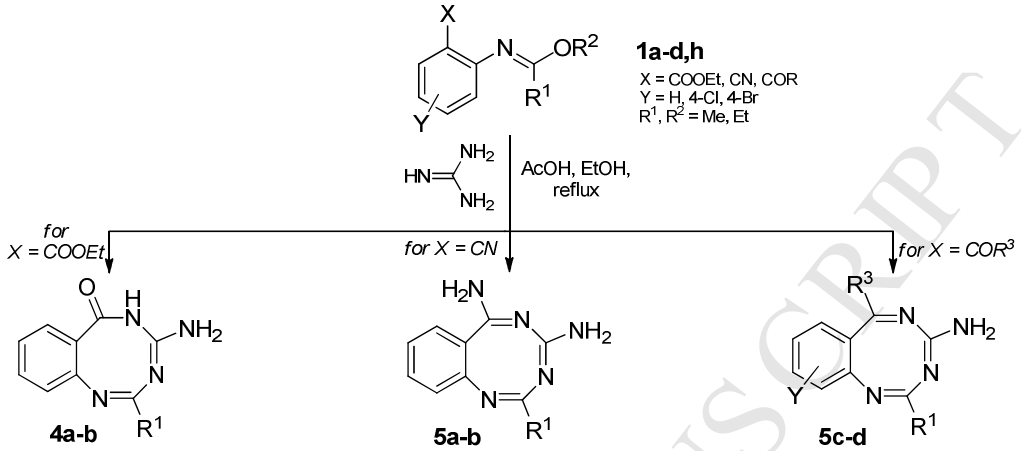
entry	Acid catalyst	T°C	$HN=C(NH_2)_2$ (n equiv)	Time (h)	Yields (%)[a]
1	-	25	1.0	12	-[b]
2	-	25	1.6	12	-[b]
3	-	79	1.6	12	-[b]
4	HCOOH	25	1.6	24	-[c]
5	HCOOH	79	1.6	24	-[c]
6	APTS	25	1.6	24	-[b]
7	APTS	79	1.6	24	-[b]
8	AcOH	25	1.6	24	**6**
9	AcOH	79	1.6	24	**39**
10	**AcOH**	**79**	**2.0**	**24**	**63**
11	AcOH	79	2.0	48	**57**[d]

[a]Isolated yield after purification by precipitation and successive washes in Et_2O. [b] **1a** was recovered unchanged. [c]degradation of **1a** was observed. [d] degradation of **4a** was observed by refluxing for 48h.

The optimized conditions (entry 10) were applied starting from iminoesters **1a-f** for the preparation of various benzotriazocines (table 5). Thus 4-amino-benzo[*f*][1,3,5]triazocin-6(5*H*)-ones **4a-b** were easily obtained from iminoesters **1a** and **b** in 63 and 69% yield respectively.

Concerning reaction from iminoesters **1c-d**, the nucleophilic addition of guanidine on the cyano moiety allowed the expected ring closure to happen. Interestingly, the structure of the new promising derivatives **5a** and **5b** (53 and 66% yield respectively) features a second amino group in position-6, that appears to be an asset for further functionalization. Finally, iminoesters **1e-f**, bearing a carbonyl function, afforded very good results, and the expected 8-membered heterocycles were isolated in 78 and 59% respectively. Here, the dehydration of hydroxylated intermediates resulting from the cyclocondensation step was easily carried out and led spontaneously to the expected aromatic systems.

Table 5. Preparation of benzotriazocines **4a-b** and **5a-d.**



	R^1	Yield (%)[a]		R^1	Yield (%)[a]		R^1	R^3	Y	Yields (%)[a]
4a	Me	**63**	**5a**	Me	**53**	**5c**	Et	Ph	8-Cl	**78**
4b	Et	**69**	**5b**	Et	**66**	**5d**	Me	Me	H	**59**

[a] Isolated yield after purification by precipitation and successive washes in Et_2O.

3. Conclusion

To conclude, we proposed here short and convenient routes to various functionalized benz[*e*][1,2,4]- or [1,2,6]oxadiazepines and benzo[*f*][1,3,5]triazocines, in good overall yields, starting from readily available arylamines (in 49-79% and 45-72% yields respectively). Besides, we highlighted the importance to have a second electrophilic substituent to direct the ring closure towards the [1,2,4]- or [1,2,6]-isomers of benzoxadiazepines. Moreover, the entitled condensed heterocycles prove to be versatile substrates to envision subsequent functionalization involving, for examples, *N*-alkylation or acylation, regioselective lithiation/electrophilic trapping sequences as well as Pd-catalyzed cross couplings.

4. Experimental section

4.1. General Methods:

The ^{1}H and ^{13}C NMR spectroscopic data were recorded at 250 MHz for ^{1}H NMR and 63 MHz for ^{13}C NMR, and $CDCl_3$ with TMS as the internal standard (for ^{1}H NMR) or DMSO-d_6 were used as solvent. HRMS spectra were recorded on a micrOTOF-Q spectrometer. MS data were recorded on a GC–MS-QP2010 spectrometer. Melting temperatures were recorded with a thermostatic oil bath device. All reagents were commercially available and purified by distillation when necessary.

*4.2. General procedure for the synthesis of iminoesters (**1a-h**).*

To a solution of selected arylamine (30 mmol, 1.0 equiv.) and appropriate orthoester (50.0 mmol, 1.7 equiv.) were added few drops of acetic acid. The resulting mixture was then stirred at reflux for 5 h. Reaction was monitored by TLC (ethyl acetate/ cyclohexane 1/9). Purification by reduced pressure distillation (0.1 mmHg) afforded the expected compounds as oils.

*4.2.1. Ethyl N-(2-carbethoxyphenyl)acetimidate (**1a**).*

Yield **84%**. bp 113 °C (0.1 mmHg); ^{1}H NMR δ_H (250 MHz, $CDCl_3$) 1.27 (t, 3H, $^3J_{HH}$ = 6.0 Hz, $\underline{CH_3}CH_2$), 1.34 (t, 3H, $^3J_{HH}$ = 9.0 Hz, $\underline{CH_3}CH_2$), 3.69-3.74 (m, 2H, CH_2), 4.20-4.27 (m, 2H, CH_2); 6.67-7.90 (m, 4H, H_{arom}); ^{13}C NMR δ_C (63 MHz, $CDCl_3$) 14.2, 15.2, 16.7, 18.3, 57.3, 60.5, 121.9, 122.6, 131.1, 132.8, 150.1, 160.6, 166.6.

*4.2.2. Methyl N-(2-carbethoxyphenyl)propionimidate (**1b**).*

Yield **92%**. bp 123 °C (0.1 mmHg); ^{1}H NMR δ_H (250 MHz, $CDCl_3$) 1.02 (q, 3H,$^3J_{HH}$ = 6.0 Hz, $\underline{CH_3}$-CH_2-C=N), 1.30 (t, 3H, $^3J_{HH}$ = 9.0 Hz, $\underline{CH_3}CH_2O$), 2.05-2.11 (m, 2H, $\underline{CH_2}CH_3$), 3.81 (s, 3H, CH_3O), 4.22-4.37 (m, 2H, CH_2O), 6.54-7.90 (m, 4H, H_{arom}); ^{13}C NMR δ_C (63 MHz, $CDCl_3$) 10.1, 14.1, 23.8, 53.2, 60.3, 115.8, 124.3, 127.1, 127.8, 133.6, 134.1, 144.2, 166.3, 168.0.

*4.2.3. Ethyl N-(2-cyanophenyl)acetimidate (**1c**).*

Yield **85%**. bp 137 °C (0.1 mmHg); ^{1}H NMR δ_H (250 MHz, $CDCl_3$) 1.26-1.32 (m, 3H, $\underline{CH_3}CH_2O$), 1.78 (s, 3H, $\underline{CH_3}$-C=N), 4.22-4.29 (m, 2H, $\underline{CH_2}$-O), 6.78–7.50 (m, 4H, H_{arom}); ^{13}C NMR δ_C (63 MHz, $CDCl_3$) 13.9, 20.0, 62.2, 105.0, 117.3, 121.7, 123.0, 132.6, 133.1, 152.4, 162.4.

*4.2.4. Methyl N-(2-cyanophenyl)propionimidate (**1d**).*

Yield **89%**. bp 145 °C (0.1 mmHg); ^{1}H NMR δ_H (250 MHz, $CDCl_3$) 1.10 (t, 3H, $^3J_{HH}$ = 7.0 Hz, $\underline{CH_3}CH_2$), 2.17 (q, 2H, $^3J_{HH}$ = 7.0 Hz, CH_2), 3.82 (s, 3H, CH_3O), 6.84-7.57 (m, 4H, H_{arom}); ^{13}C NMR δ_C (63 MHz, $CDCl_3$) 10.2, 23.1, 53.2, 104.9, 110.6, 115.9, 122.6, 133.7, 150.6, 163.7, 166.5, 167.9.

*4.2.5. Methyl N-(2-benzoyl-4-chlorophenyl)propionimidate (**1e**).*

Yield **93%**. bp 209 °C (0.1 mmHg); ^{1}H NMR δ_H (250 MHz, $CDCl_3$) 0.98 (t, 3H, $^{3}J_{HH}$ = 9.0 Hz, $\underline{CH_2}CH_2C$=N), 2.07 (q, $^{3}J_{HH}$ = 9.0 Hz, 2H, CH_2), 3.23 (s, 3H, CH_3O), 6.72-7.77 (m, 8H, H_{arom}); ^{13}C NMR δ_C (63 MHz, $CDCl_3$) 10.3, 23.7, 53.1, 118.5, 123.3, 128.0, 128.3, 128.9, 129.0, 129.6, 131.3, 132.8, 134.0, 137.3, 145.8, 165.4, 196.0.

*4.2.6. Ethyl N-(2-acetylphenyl)acetimidate (**1f**).*

Yield **96%**. bp 121 °C (0.1 mmHg); ^{1}H NMR δ_H (250 MHz, $CDCl_3$) 1.35 (t, 3H, $^{3}J_{HH}$ = 7.0 Hz, $\underline{CH_3}CH_2$), 1.76 (s, 3H, CH_3C=N), 2.49 (s, 3H, CH_3CO), 4.25 (q, 2H, $^{3}J_{HH}$ = 7.0 Hz, CH_2), 6.70-7.68 (m, 4H, H_{arom}); ^{13}C NMR δ_C (63 MHz, $CDCl_3$) 14.6, 17.0, 30.7, 62.1, 122.7, 123.1, 129.6, 131.6, 132.8, 146.7, 161.8, 201.3.

*4.2.7. Methyl N-(2-acetylphenyl)propionimidate (**1g**).*

Yield **94%**. bp 122 °C (0.1 mmHg); ^{1}H NMR δ_H (250 MHz, $CDCl_3$) 1.03 (t, 3H, $^{3}J_{HH}$ = 7.0 Hz, CH_3CH_2), 2.11 (q, 2H, $^{3}J_{HH}$ = 7.0 Hz, CH_2), 2.50 (s, 3H, CH_3CO), 3.83 (s, 3H, OCH_3), 6,61-7,69 (m, 4H, H_{arom}); ^{13}C NMR δ_C (63 MHz, $CDCl_3$) 10.7, 24.0, 30.8, 53.7, 116.0, 117.5, 122.7, 129.6, 132.8, 148.3, 165.2, 201.29.

*4.2.8. Methyl N-(2-carbomethoxy-4-bromophenyl)propionimidate (**1h**).*

Yield **81%**. bp 127 °C (0.1 mmHg); ^{1}H NMR δ_H (250 MHz, $CDCl_3$) 1.06 (t, 3H, $^{3}J_{HH}$ = 7.0 Hz, CH_3CH_2), 2.09 (q, 2H, $^{3}J_{HH}$ = 7.0 Hz, CH_2), 3.59 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 6,64-8.04 (m, 3H, H_{arom}); ^{13}C NMR δ_C (63 MHz, $CDCl_3$) 10.3, 21.1, 51.1, 52.8, 118.0, 122.1, 123.9, 134.1, 136.9, 144.2, 165.7, 170.9.

*4.3. General procedure for the synthesis of benzoxadiazepines (**2a-e**) and (**3a-c**).*

Hydroxylamine hydrochloride (0.34 g, 50.0 mmol, 1.0 equiv) in ethanol (EtOH) (5 mL) was added to a solution of sodium ethylate (0.12 g, 50.0 mmol, 1.0 equiv) in EtOH (4 mL) at 0 °C, under nitrogen atmosphere. After stirring and filtration, free hydroxylamine in EtOH was then obtained. Then, to a solution of iminoesters **1a-h** (3.0 mmol, 1.0 equiv) in EtOH (4 mL) was added hydroxylamine (6.0 mmol, 2.0 equiv). Reaction mixture was stirred for 24 h at room temperature. After solvent evaporation, crude product was obtained by precipitation in petroleum ether and then purification was carried out by successive washings with diethyl ether (Et_2O). The expected products **2a-e** and **3a-c** were obtained as solid.

*4.3.1. 2-Methyl benz[e][1,2,4]oxadiazepin-5(3H)-one (**2a**).*

Yield **58%**. m.p. 159-161 °C; ^{1}H NMR δ_H (250 MHz, DMSO-d_6) 2.63 (s, 3H, CH_3), 7.48-7.55 (m, 1H, H_{arom}), 7.64-7.69 (m, 2H, H_{arom}), 8.20 (d, 1H, $^{3}J_{HH}$ = 8.0 Hz, H_{arom}), 8.46 (brs, 1H, NH); ^{13}C NMR δ_C (63 MHz, DMSO-d_6) 21.0, 113.2, 123.2, 126.9, 128.1, 131.7, 141.3, 150.9, 155.5; ESI-HRMS calcd for $C_9H_8N_2O_2$ (M): 176.0828, found: 176.0843.

*4.3.2. 2-Ethyl benz[e][1,2,4]oxadiazepin-5(3H)-one (**2b**).*

Yield **61%**. m.p. 171-173 °C; ^{1}H NMR δ_H (250 MHz, DMSO-d_6) 1.29 (t, 3H, $^{3}J_{HH}$ = 7.0 Hz, CH_3), 3.01 (q, 2H, $^{3}J_{HH}$ = 7.0Hz, CH_2), 7.39-7.43 (m, 1H, H_{arom}), 7.61-7.74 (m, 1H, H_{arom}), 8.02 (d, 1H, $^{3}J_{HH}$ = 8.0 Hz, H_{arom}); ^{13}C NMR δ_C (63 MHz, DMSO-d_6) 10.95, 26.34, 118.63, 125.04, 125.85, 127.58, 132.46, 145.32, 158.15, 161.68. ESI-HRMS calcd for $C_{10}H_{10}N_2O_2$ $(M+H)^+$: 191.0815, found: 191.0866.

*4.3.3. 7-Bromo-2-ethyl benz[e][1,2,4]oxadiazepin-5(3H)-one (**2c**).*

Yield **74%**. m.p 176-178 °C; ^{1}H NMR δ_H (250 MHz, DMSO-d_6 D_2O) 1.22 (t, 3H, $^{3}J_{HH}$ = 7.0 Hz, CH_3), 2.85 (q, 2H, $^{3}J_{HH}$ = 7.0 Hz, CH_2), 7.55 (d, 1H, $^{3}J_{HH}$ = 9.0 Hz, H_{arom}), 7.81 (dd, 1H, $^{3}J_{HH}$ = 9.0 Hz, $^{4}J_{HH}$ = 4.5 Hz, H_{arom}), 8.04 (d, 1H, $^{3}J_{HH}$ = 4.5 Hz, H_{arom}); ^{13}C NMR δ_C (63 MHz, DMSO-d_6) 10.2, 25.8, 117.3, 122.5, 127.3, 129.1, 135.4, 144.5, 157.7, 159.3; ESI-HRMS calcd for $C_{10}H_9BrN_2O_2$ $(M+H^+)$: 271.2353, found: 271.2436.

*4.3.4. 2-Methyl benz[e][1,2,4]oxadiazepin-5(3H)-imine (**2d**).*

Yield **61%**. m.p 145-147 °C; ^{1}H NMR δ_H (250 MHz, DMSO-d_6 D_2O) 2.61 (s, 3H, CH_3); 7.35-7.43 (m, 1H, H_{arom}), 7.59-7.71 (m, 2H, , H_{arom}), 8.11 (d, 1H, $^{3}J_{HH}$ = 7.0 Hz, H_{arom}); ^{13}C NMR δ_C (63 MHz, DMSO-d_6) 21.1, 118.7, 125.0, 125.1, 125.9, 127.4, 132.6, 145.4, 154.8, 161.6, 161.7; ESI-HRMS calcd for $C_9H_9N_3O$ $(M+2H^+)$: 177.0699, found: 177.0659.

*4.3.5. 2-Ethyl benz[e][1,2,4]oxadiazepin-5(3H)-imine (**2e**).*

Yield **79%**. m.p 161-163 °C; ^{1}H NMR δ_H (250 MHz, DMSO-d_6) 1.29 (t, 3H, $^{3}J_{HH}$ = 8.0 Hz, CH_3), 3.04 (q, 2H, $^{3}J_{HH}$ = 8.0 Hz, CH_2), 7.52 (t, 1H, $^{3}J_{HH}$ = 8.0Hz, H_{arom}), 7.65-7.75 (m, 2H, H_{arom}), 8.21 (d, 1H, $^{3}J_{HH}$ = 8.0 Hz, H_{arom}), 8.43 (s, 2H, NH); ^{13}C NMR δ_C (63 MHz, DMSO-d_6) 10.8, 26.2, 113.1, 123.2, 126.9, 128.3, 131.7, 141.3, 150.8, 158.76; ESI-HRMS calcd for $C_{10}H_{11}N_3O$ $(M+H^+)$: 190.0991, found: 190.0975.

*4.3.6. 7-Chloro-2-ethyl-5-phenyl benz[d][1,2,6]oxadiazepine (**3a**).*

Yield **85%**. m.p 188-190 °C; ^{1}H NMR δ_H (250 MHz, $CDCl_3$) 1.47 (t, 3H, $^{3}J_{HH}$ = 7.0 Hz, CH_3), 3.26 (q, 2H, $^{3}J_{HH}$ = 7.0 Hz, CH_2), 7.36-7.62 (m, 7H, H_{arom}), 7.93 (d, 1H, $^{3}J_{HH}$ = 8.0 Hz, H_{arom}); ^{13}C NMR δ_C (63 MHz, $CDCl_3$) 10.2, 26.1, 123.7, 124.5, 128.9, 129.0, 129.1, 129.5, 130.1, 130.5, 131.4, 134.7, 138.9, 149.0, 162.1; ESI-HRMS calcd for $C_{16}H_{13}ClN_2O$ $(M+H^+)$: 285.0820, found: 285.0789.

*4.3.7. 2,5-Dimethyl benz[d][1,2,6]oxadiazepine (**3b**).*

Yield **73%**. m.p 144-146 °C; ^{1}H NMR δ_H (250 MHz, DMSO-d_6) 2.84 (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 7.54 (t, 1H, $^{3}J_{HH}$ = 7.0 Hz, H_{arom}), 7.67 (t, 1H, $^{3}J_{HH}$ = 7.0 Hz, H_{arom}), 7.79 (d, 1H, $^{3}J_{HH}$ = 7.0 Hz, H_{arom}), 7.86 (dd, 1H, $^{3}J_{HH}$ = 7.0 Hz, $^{4}J_{HH}$ = 1.0 Hz, H_{arom}); ^{13}C NMR δ_C (63 MHz, DMSO-d_6) 13.2, 20.8, 123.4, 123.7, 128.7, 128.8, 131.0, 140.1, 150.9, 157.9; ESI-HRMS calcd for $C_{10}H_{10}N_2O$ $(M+H^+)$: 175.0866, found: 175.0883.

*4.3.8. 2-Ethyl-5-methyl benz[d][1,2,6]oxadiazepine (**3c**).*

Yield **79%**. m.p 149-151 °C; ^{1}H NMR δ_H (250 MHz, DMSO-d_6) 1.29 (t, 3H, $^{3}J_{HH}$ = 7.0 Hz, CH_3), 2.57 (s, 3H, CH_3), 3.12 (q, 2H, $^{3}J_{HH}$ = 7.0 Hz, CH_2), 7.65 (dt, 1H, $^{3}J_{HH}$ = 7.0 Hz, H_{arom}), 7.77 (t, 1H, $^{3}J_{HH}$ = 7.0 Hz, H_{arom}), 7.89 (dd, 1H, $^{3}J_{HH}$ = 7.0 Hz, $^{4}J_{HH}$ = 3.0 Hz, H_{arom}), 8.08 (dd, 1H, $^{3}J_{HH}$ = 7.0 Hz, $^{4}J_{HH}$ = 3.0 Hz, H_{arom}). ^{13}C NMR δ_C (63 MHz, DMSO-d_6) 10.6, 13.6, 26.0, 123.7, 124.4, 128.6, 129.2, 131.3, 139.2, 150.6, 160.4. ESI-HRMS calcd for $C_{11}H_{12}N_2O$ $(M+H^+)$: 189.1028, found: 189.0122.

*4.4. General procedure for the synthesis of benzotriazocines (**4a-b**) and (**5a-d**).*

Guanidinium hydrochloride (0.57 g, 6.0 mmol, 1.0 equiv) in ethanol (EtOH) (5 mL) was added to a solution of sodium ethylate (0.41 g, 6.0 mmol, 1 equiv) in EtOH (4 mL) at 0 °C, under nitrogen atmosphere. After stirring and filtration, free guanidine in EtOH was then obtained. Then, to solution of iminoesters **1a-f** (3.0 mmol, 1.0 equiv) in EtOH (4 mL) was added guanidine (6.0 mmol, 2.0 equiv), in the presence of few drops of acetic acid. Reaction mixture was refluxing for 24 h. After solvent evaporation, crude product was obtained by precipitation in petroleum ether and then purification was carried

out by successive washings with diethyl ether (Et_2O). The expected products **4a-b** or **5a-d** were obtained as solid.

*4.4.1. 4-Amino-2-methyl benzo[f][1,3,5]triazocin-6(5H)-one (**4a**).*

Yield **63%**. m.p. 192-194 °C; ^{1}H NMR δ_H (250 MHz, DMSO-d_6) 1.61 (s, 3H, CH_3), 6.34 (t, 1H, ^{3}J = 7.0 Hz, H_{arom}), 6.49 (t, 1H, ^{3}J = 7.0 Hz, H_{arom}), 6.66 (br s, 2H, NH_2), 6.88-6.96 (m, 1H, H_{arom}), 7.65-7.75 (m, 1H, H_{arom}), 8.30 (s, 1H, NH); ^{13}C NMR δ_C (63 MHz, DMSO-d_6). 25.4, 114.5, 115.8, 121.0, 130.5, 132.4, 150.7, 160.3, 167.7, 175.2. ESI-HRMS calcd for $C_{10}H_{10}N_4O$ (M): 202.0849, found: 202.1124.

*4.4.2. 4-Amino-2-ethyl benzo[f][1,3,5]triazocin-6(5H)-one (**4b**).*

Yield **69%**. m.p. 191-193 °C; ^{1}H NMR δ_H (250 MHz, DMSO-d_6) 1.24 (t, 3H, $^3J_{HH}$ = 7.0 Hz, CH_3), 2.68 (q, 2H, $^3J_{HH}$ = 7.0 Hz, CH_2), 6.00 (br s, 1H, NH), 7.37 (t, 1H, $^3J_{HH}$ = 7.0 Hz, H_{arom}), 7.57-7.65 (m, 1H, H_{arom}), 7.67 (br s, 2H, NH_2), 7.69-7.71 (m, 1H, H_{arom}), 8.14 (d, 1H, $^3J_{HH}$ = 7.0 Hz, H_{arom}); ^{13}C NMR δ_C (63 MHz, DMSO-d_6) 13.3, 32.9, 113.5, 124.1, 125.1, 127.7, 133.2, 151.0, 162.6, 168.2, 168.3. ESI-HRMS calcd for $C_{11}H_{12}N_4O$ (M): 216.1006, found: 216.1255.

*4.4.3. 2-Methyl benzo[f][1,3,5]triazocine-4,6-diamine (**5a**).*

Yield **53%** %. m.p. 168-170 °C; ^{1}H NMR δ_H (250 MHz, DMSO-d_6) 1.72 (s, 3H, CH_3), 7.46 (t, 1H, $^3J_{HH}$ = 7.0 Hz, H_{arom}), 7.66 (d, 2H, $^3J_{HH}$ = 7.0 Hz, H_{arom}), 7.78 (br s, 4H, NH_2), 8.26 (dd, 1H, $^3J_{HH}$ = 7.0 Hz, $^3J_{HH}$ = 2.0 Hz, H_{arom}); ^{13}C NMR δ_C (63 MHz, DMSO-d_6) 25.7, 113.0, 123.9, 124.9, 127.2, 133.0, 159.6, 162.2, 163.6, 176.1. ESI-HRMS calcd for $C_{10}H_{11}N_5$ (M): 202.1098, found: 202.1087.

*4.4.4. 2-Ethyl benzo[f][1,3,5]triazocine-4,6-diamine (**5b**).*

Yield **66%**. m.p. 172-174 °C; ^{1}H NMR δ_H (250 MHz, DMSO-d_6) 1.25 (t, 3H, $^3J_{HH}$ = 7.0 Hz, CH_3), 2.66 (q, 2H, $^3J_{HH}$ = 7.0 Hz, CH_2), 5.97 (br s, 2H, NH_2), 7.36 (d, 1H, $^3J_{HH}$ = 7.0 Hz, H_{arom}), 7.58-7.70 (m, 4H, H_{arom}, NH_2), 8.14 (d, 1H, $^3J_{HH}$ = 7.0 Hz, H_{arom}); ^{13}C NMR δ_C (63 MHz, DMSO-d_6) 13.3, 32.9, 113.5, 124.1, 125.1, 127.7, 133.2, 151.0, 162.6, 168.3, 176.1. ESI-HRMS calcd for $C_{11}H_{13}N_5$ ($M+H^+$): 216.1224, found: 216.1229.

*4.4.5. 8-Chloro-2-ethyl-6-phenyl benzo[f][1,3,5]triazocin-4-amine (**5c**).*

Yield **78%**. m.p. 178-180 °C; ^{1}H NMR δ_H (250 MHz, DMSO-d_6) δ_H = 1.39 (t, 3H, $^3J_{HH}$ = 7.0 Hz, CH_3), 4.48 (q, 2H, $^3J_{HH}$ = 7.0 Hz, CH_2), 5.94 (br s, 1H, NH_2), 6.96 (br s, 1H, NH_2), 7.51-7.58 (m, 6H, H_{arom}), 7.69 (dd, 1H, $^3J_{HH}$ = 2.0 Hz$^3J_{HH}$ = 7.0 Hz, H_{arom}), 7.84 (d, 1H, $^3J_{HH}$ = 7.0 Hz, H_{arom}); ^{13}C NMR δ_C (63 MHz, DMSO-d_6) 14.9, 62.1, 114.1, 124.5, 124.7, 129.0, 129.3 (2C), 129.4 (2C), 129.6, 129.9, 130.5, 136.8, 145.6, 150.5, 162.0. ESI-HRMS calcd for $C_{17}H_{15}ClN_4$ ($M+H^+$): 311.1058, found: 311.052.

*4.4.6. 2,6-Dimethyl benzo[f][1,3,5]triazocin-4-amine (**5d**).*

Yield **59%**. m.p. 166-168 °C; ^{1}H NMR δ_H (250 MHz, DMSO-d_6) δ_H = 2.11 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 5.00 (br s, 2H, NH_2), 7.08 (t, 1H, $^3J_{HH}$ = 8.0 Hz, H_{arom}), 7.14 (d, 1H, $^3J_{HH}$ = 8.0 Hz, H_{arom}), 7.26 (d, 1H, $^3J_{HH}$ = 7.0 Hz, H_{arom}),7.71 (d, 1H, $^3J_{HH}$ = 7.0 Hz, H_{arom});^{13}C NMR δ_C (63 MHz, DMSO-d_6) 13.5, 15.8, 116.9, 121.6, 124.8, 127.1, 129.2, 139.4, 141.9, 160.24, 163.8. ESI-HRMS calcd for $C_{11}H_{12}N_4$ ($M+H^+$): 201.1104, found: 201.1080.

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