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A one-pot three-component reaction providing tricyclic 1,4-benzoxazepine derivatives

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ABSTRACT

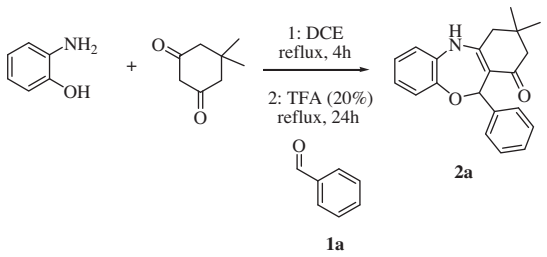
A new one-pot, three-component reaction of aromatic aldehydes, 2-aminophenol, and dimedone for the synthesis of tricyclic 1,4-benzoxazepine derivatives in moderate to good yields is described.

Multicomponent reactions (MCRs) are processes in which at least three different simple substrates react in one-pot to give the target materials.[1] These reactions, which have gained significant attention during the past years, do not occur through a single-step procedure, but rather via several sequential steps involving cascades or domino reactions.[2] Simplicity, greater efficiency, and atom economy with generation of molecular complexity and diversity in one-pot transformations are some advantages of these reactions.[3]

Benzo-fused seven-membered heterocycles containing two heteroatoms at positions 1 and 4 are used in medicinal chemistry due to their wide spectrum of biological activities.[4] Examples include 1,4-benzodioxepine, 1,4-benzodithiepine, 1,4-benzoxazepine, 1,4-benzoxathiepine, 1,4-benzothiazepine, and 1,4-benzodiazepine.[5] Benzodiazepines and benzoxazepines are known as non-peptide vasopressin V2 receptor agonists.[5] Benzoxazepine derivatives form an important class of compounds with various biological activities.[6] Among compounds containing this fragment are psychotropic and neurotropic agents,[7] a non-nucleoside HIV-1 reverse transcriptase inhibitor,[8] calcium antagonists,[9] antidepressants,[10] and analgesics.[11]

Herein, we report a one-pot, three-component synthesis of 1,4-benzoxazepine derivatives via the multicomponent reaction of commercially available 2-aminophenol, dimedone, and various aromatic aldehydes. To our delight, the reaction of preheated 2-aminophenol and dimedone in DCE with benzaldehyde proceeded smoothly to completion within 24 h in the presence of trifluoroacetic acid (TFA) (20 mol %), affording the tricyclic 1,4-benzoxazepine **2a** in 68% yield (Scheme 1).[12] The analytical and spectroscopic data of **2a** were in agreement with the proposed structure.[13] For example, the ^{1}H NMR spectrum of **2a** contained characteristic singlets at δ 1.06, 1.09, 2.65, 6.53, and 9.21 due to the two methyl groups, CH_2CO, CHPh, and NH protons, respectively, together with an AB quartet at δ 2.18 for the $CH_2C{=}C$ group. The ^{13}C NMR spectrum of **2a** exhibited 21 distinct signals including one at δ 192.6 due to the C=O group.

We next examined the substrate scope by reacting 2-aminophenol and dimedone with different aldehydes in DCE (Scheme 2). As indicated in Table 1, reactions of various aldehydes **1a–l** afforded the corresponding 1,4-benzoxazepine derivatives **2a–l**. Gratifyingly, aldehydes with electron-donating or electron-withdrawing groups underwent this multicomponent sequence (Table 1).[14]



Scheme 1. Synthesis of 1,4-benzoxazepine **2a**.

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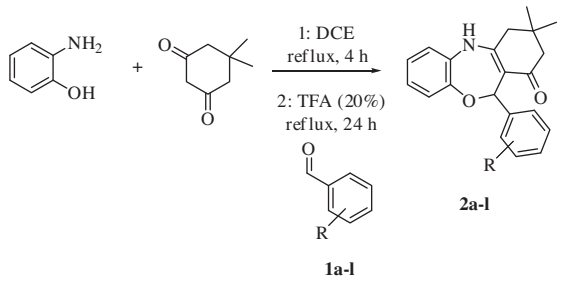


Scheme 2. Synthesis of 1,4-benzoxazepine derivatives **2a–l**.

Table 1
Isolated yields of 1,4-benzoxazepines **2a–l**

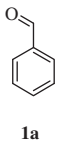
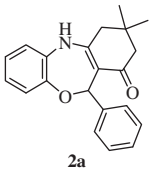
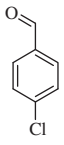
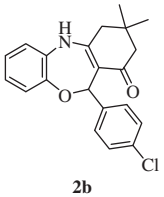
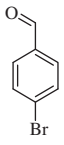
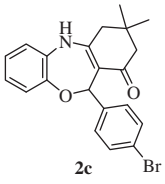
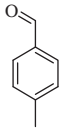
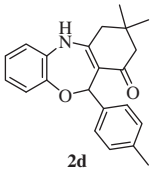
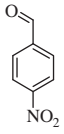
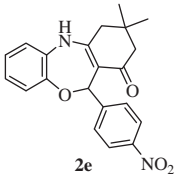
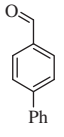
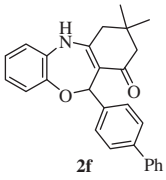
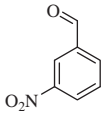
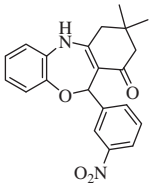
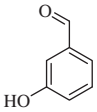
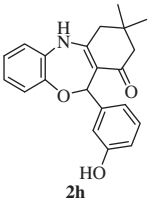
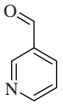
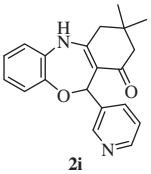
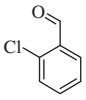
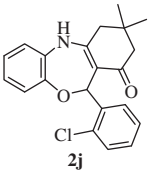
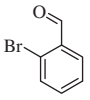
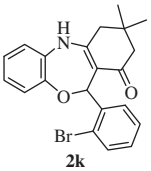
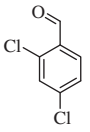
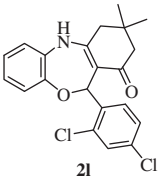
Entry	Aldehyde	Product	Yield (%)
1	 **1a**	 **2a**	68
2	 **1b**	 **2b**	77
3	 **1c**	 **2c**	73
4	 **1d**	 **2d**	63
5	 **1e**	 **2e**	82
6	 **1f**	 **2f**	65
7	 **1g**	 **2g**	78

Table 1 (*continued*)

Entry	Aldehyde	Product	Yield (%)
8	 **1h**	 **2h**	58
9	 **1i**	 **2i**	59
10	 **1j**	 **2j**	73
11	 **1k**	 **2k**	69
12	 **1l**	 **2l**	75

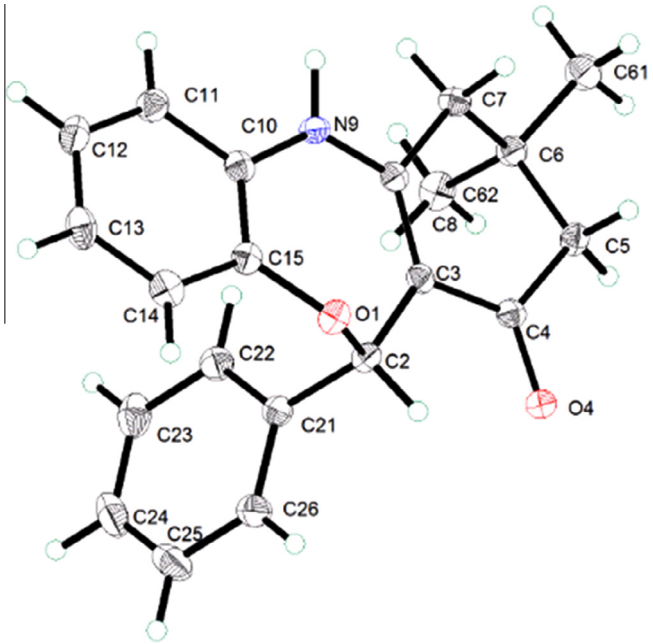
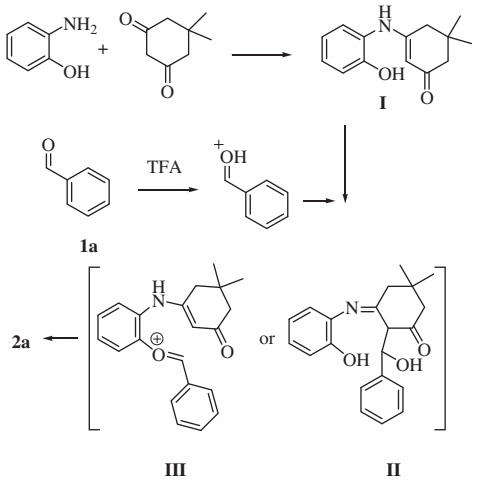


Figure 1. X-ray crystal structure of compound **2a**.



Scheme 3. Suggested mechanism for the formation of **2a**.

Unambiguous evidence for the structure of **2a** was obtained by single-crystal X-ray-diffraction analysis (Fig. 1).[15]

Mechanistically, the reaction presumably proceeds via the initial formation of the enamine **I**, produced from condensation of 2-aminophenol with dimedone. Subsequent trapping with aldehyde **1a** via either the intermediate imine **II**[16] or oxonium ion **III**,[17] and intramolecular cyclization finally afford **2a** (Scheme 3).

Inspection of the results revealed that whereas an unsubstituted aldehyde afforded **2a** in moderate yield (entry 1 Table 1), those bearing electron-withdrawing groups produced the corresponding products in higher yields (entries 2, 3, 5, 7, and 10, Table 1). On the other hand, lower yields of 1,4-benzoxazepines were obtained by introducing electron-donating groups on the aromatic aldehyde (entries 4, 6, and 8, Table 1). This behavior supports the suggested mechanism since the introduction of an electron-withdrawing group on the phenyl ring accelerates the rate of formation or consumption of either intermediates **II** or **III**.

In conclusion, a range of 1,4-benzoxazepines **2a–l** has been synthesized in moderate to high yields via the one-pot, three-component reaction of 2-aminophenol, dimedone, and aldehydes **1a–l**. These new compounds broaden the scope of MCRs and may be of potential interest in drug discovery.

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12. *General procedure for the synthesis of 1,4-benzoxazepine* ***2a****.* A stirred solution of 2-aminophenol (0.109 g, 1 mmol) and dimedone (0.168 g, 1.2 mmol) in DCE (5 mL) was heated at reflux for 4 h. After completion of this step as indicated by TLC, benzaldehyde (0.106 g, 1 mmol) and TFA (0.023 g, 0.2 mmol) were added and heating at reflux was continued for 24 h. After completion, aqueous $NaHCO_3$ (10 mL, 20%) was added and the organic phase was separated, washed with H_2O (10 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was recrystallized from 30% EtOAc in hexane.
13. *3,3-Dimethyl-11-phenyl-3,4,5,11-tetrahydrodibenzo[b,e][1,4]oxazepin-1(2H)-one (****2a****).* White solid: (398 mg, 68%); mp: 269–271 °C; IR (KBr) *v*: 3344 (NH), 1739 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.06 (s, 3H, Me), 1.09 (s, 3H, Me), 2.18 (AB quartet, 2H, J = 16.0 Hz, C=CCH_2), 2.65 (s, 2H, CH_2CO), 6.53 (s, 1H, CHPh), 6.61 (d, 1H, J = 7.3 Hz, Ar), 6.70 (t, 1H, J = 7.3 Hz, Ar), 6.82 (dd, 1H, J = 7.5 Hz, Ar), 7.03 (d, 2H, J = 8.5 Hz, Ar), 7.42–7.47 (m, 3H, Ar), 7.57 (d, 1H, J = 6.3 Hz, Ar), 9.21 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 27.6, 28.2, 31.8, 43,7, 49.3, 78.5, 104.4, 145.8, 116.3, 118.0, 119.0, 123.4, 123.9, 128.0, 130.1, 132.2, 134.0, 138.7, 149.0, 154.9, 192.6 (CO); MS (El) *m*/*z*: 319 (92, M^+), 318 (100), 242 (30), 234 (14), 77 (23); Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.54; H, 6.98; N, 4.45.
14. *11-([1,1′-Biphenyl]-4-yl)-3,3-dimethyl-3,4,5,11-tetrahydrodibenzo[b,e][1,4]oxazepin-1(2H)-one (****2f****).* White solid: (395 mg, 65%); mp 277–279 °C; IR (KBr) *v*: 3324 (NH), 1741 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.10 (s, 3H, Me), 1.11 (s, 3H, Me), 2.21 (AB quartet, 2H, J = 15.9 Hz, C=CCH_2), 2.68 (s, 2H, CH_2CO), 6.62 (s, 1H, *CH*Ph), 6.67 (d, 1H, J = 7.8 Hz, Ar), 6.76–6.83 (m, 2H, Ar), 7.04 (d, 1H, J = 7.7 Hz, Ar), 7.18 (d, 2H, J = 8.1 Hz, Ar), 7.29 (t, 1H, J = 7.1 Hz, Ar), 7.38 (t, 2H, J = 7.1 Hz, Ar), 7.47 (d, 2H, J = 8.1 Hz, Ar), 7.55 (d, 2H, J = 7.29 Hz, Ar), 9.19 (s, 1H, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6) δ 27.5, 28.4, 31.9, 43.6, 49.4, 78.8, 109.4, 120.2, 122.8, 123.2, 123.9, 126.2, 126.5, 126.7, 127.2, 127.4, 128.8, 128.9, 129.0, 129.2, 134.0, 138.9, 139.1, 139.3, 146.0, 154.8, 192.6 (CO); MS (El) *m*/*z*: 395 (81, M^+), 394 (100), 318 (41), 242 (40), 234 (7); Anal. Calcd for $C_{27}H_{25}NO_2$: C, 82.00; H, 6.37; N, 3.54. Found: C, 82.27; H, 6.44; N, 3.41.
15. CCDC-921136. Copies of these data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk).
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