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'On water' synthesis of 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines catalysed by sodium dodecyl sulfate (SDS)

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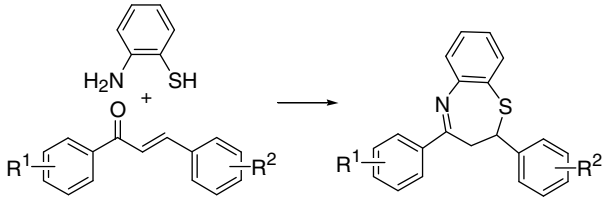
ABSTRACT

An efficient synthesis of 1,3-diaryl-2,3-dihydro-1,5-benzothiazepines has been developed by the reaction of various 1,3-diaryl-2-propenones with 2-aminothiophenol in water under neutral conditions catalysed by SDS. Excellent chemoselectivity was observed for substrates possessing halogen atoms or nitro/alkoxy/thioalkyl groups which did not undergo competitive aromatic nucleophilic substitution of the halogen atoms or the nitro group, reduction of the nitro or the α,β-unsaturated carbonyl group, or dealkylation of the alkoxy/thioalkoxy groups.

The broad spectrum of biological activity[1] of compounds bearing the 1,5-benzothiazepine moiety has stimulated interest in developing new synthetic protocols for their synthesis (Scheme 1).[2,3] There remains the necessity to develop a more effective and convenient synthetic procedure as the reported methods have one or more disadvantages such as the use of a high boiling solvent (e.g., DMF) that is difficult to recover, excess amounts of acid or base, special apparatus, corrosive (e.g., HCl gas, TFA) and hazardous (e.g., pyridine, piperidine, halogenated hydrocarbon) reagents/solvents and special efforts to prepare the catalysts and adsorb the reactants onto a solid support.

The increasing concern about the tight legislation on the maintenance of greenness in synthetic pathways/processes[4] led us to develop a method using a reagent that is less hazardous and can be used in catalytic amounts and water as solvent as an alternative to volatile organic solvents. Water as a reaction medium has gained importance in the development of sustainable chemistry.[5] In continuation of our efforts in developing 'On Water' synthetic methodologies[6], we report a convenient synthesis of 1,5-benzothiazepines in water.



Scheme 1. Synthesis of 2,3-dihydro-1,5-benzothiazepines.

The commonly adopted strategy for the synthesis of benzothiazepines involves cyclocondensation of 1,3-diarylpropenones with 2-aminothiophenol (Scheme 1). Our initial efforts on the reaction of 1,3-diphenylpropenone (**1**) with 2-aminothiophenol (**2**) under neat conditions at 110 °C (oil-bath) for 12 h did not produce any significant amount of 1,3-diphenyl-2,3-dihydro-1,5-benzothiazepine (**3**). When the reaction was carried out in water under reflux (oil-bath temperature 110 °C) for 12 h, **3** was formed in 15% yield. Recently, it has been demonstrated that the yields in carrying out the reaction in aqueous medium were superior in brine than those in water.[7] When we used brine, benzothiazepine **3** was obtained in 18% yield. We realised that the presence of the aryl rings attribute hydrophobic character to **1** and in a biphasic system the interactions required for the reaction to occur are not attained. Hence, we thought that the use of a surface-active agent as a catalyst/additive may be beneficial as it would assemble with the reactants through hydrophobic interactions excluding the water molecules from the organic phase forming micelles.[8] We were happy to note that treatment of **1** (1 mmol) with **2** (1.1 mmol) in water (5 mL) at 110 °C (oil-bath) for 12 h in the presence of SDS (1 mmol) afforded **3** in 65% yield. The use of 50, 10 and 5 mol % of SDS resulted in the formation of **3** in 65%, 65%

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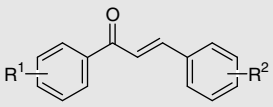
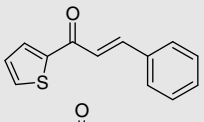
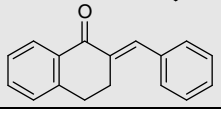
and 40% yields, respectively, under similar conditions indicating that a 10 mol % amount of SDS is the critical amount required for the cyclocondensation. The use of brine as the reaction medium instead of water afforded comparable yields in the presence of SDS (10 mol %). The use of water as the reaction medium was found to be necessary as the treatment of **1** with **2** in the presence of SDS (10 mol %) at 110 °C (oil-bath) for 12 h under neat conditions afforded **3** in only 20% yield.

To establish the generality of this method, we investigated the cyclocondensation of various substituted 1,3-diarylpropenones with **2**. The starting 1,3-diarylpropenones were prepared by the Claisen–Schmidt condensation between various substituted aryl methyl ketones with aryl aldehydes following the $LiOH{\cdot}H_2O$ catalysed dual activation procedure.[9] The reaction of various 1,3-diarylpropenones with **2** afforded the corresponding 1,3-diaryl-2,3-dihydro-1,5-benzothiazepines in 61–79% yields (Table 1). The reaction was compatible with various electron-donating (Me, OMe and SMe) and electron-withdrawing (Br, Cl, F, NO_2 and SO_2Me) substituents as well as heteroaryl rings. Substrates with halogen atoms[10] (Table 1, entries 2–6, 10, 12 and 18–20) and NO_2groups[11] (Table 1, entries 7–9 and 14) did not undergo aromatic nucleophilic substitution. The NO_2[12] and the α,β-unsaturated carbonyl[13] groups were not reduced although thiols possess single electron transfer properties.[14] For substrates with aryl alkyl ether/thioether (Table 1, entries 11–20) groups, no *O*/*S*-dealkylation took place.[15,16] The best results were obtained when the reactions were carried out as follows: the 1,3-diarylpropenone in water was heated under reflux (oil-bath temp 110 °C) under magnetic stirring until it formed a melt and mixed with water as tiny droplets. 2-Aminothiophenol **2** was added followed by SDS (10 mol %), and the mixture was heated under reflux (oil-bath temp 110 °C). When the reactants and SDS were added together, a solid formed which settled at the bottom of the flask resulting in lower yields due to incomplete consumption of the starting materials.

In conclusion, we have described a convenient synthesis of 1,3-diaryl-2,3-dihydro-1,5-benzothiazepines by the reaction of 1,3-diaryl-2-propenones with 2-aminothiophenol in water catalysed by SDS.[17] The substantial rate acceleration in carrying out the reaction of insoluble substrates in aqueous medium makes this protocol an 'on water'[18] synthesis. The advantages are the use of a cheap, easy to handle and commercially available catalyst and water as the reaction medium in place of harmful volatile organic solvents.

Table 1
Synthesis of 2,3-dihydro-1,5-benzothiazepines[a]

Entry	Substrate	Time (h)	Yield[b,c] (%)
			
1	$R^1 = R^2 = H$	12	65
2	$R^1 = H$; $R^2 = 4\text{-Cl}$	10	72
3	$R^1 = 4\text{-Cl}$; $R^2 = H$	12	76
4	$R^1 = H$; $R^2 = 4\text{-F}$	12	79
5	$R^1 = 4\text{-F}$; $R^2 = H$	12	75
6	$R^1 = 4\text{-Br}$; $R^2 = H$	12	76
7	$R^1 = 4\text{-NO}_2$; $R^2 = H$	10	71
8	$R^1 = H$; $R^2 = 4\text{-NO}_2$	16	72
9	$R^1 = H$; $R^2 = 2\text{-NO}_2$	16	72
10	$R^1 = 4\text{-Cl}$; $R^2 = 2\text{-F}$	8	64
11	$R^1 = H$; $R^2 = 4\text{-OMe}$	12	65
12	$R^1 = 4\text{-Cl}$; $R^2 = 4\text{-OMe}$	12	74
13	$R^1 = 4\text{-Me}$; $R^2 = 4\text{-OMe}$	12	61
14	$R^1 = 4\text{-NO}_2$; $R^2 = 4\text{-OMe}$	10	66
15	$R^1 = H$; $R^2 = 4\text{-SMe}$	10	65
16	$R^1 = 4\text{-SMe}$; $R^2 = 4\text{-Me}$	8	71
17	$R^1 = 4\text{-CF}_3$; $R^2 = 4\text{-SMe}$	6	73
18	$R^1 = 4\text{-Cl}$; $R^2 = 4\text{-SMe}$	12	68
19	$R^1 = 4\text{-SMe}$; $R^2 = 4\text{-Cl}$	10	64
20	$R^1 = 4\text{-SMe}$; $R^2 = 4\text{-F}$	6	68
21	$R^1 = 4\text{-CF}_3$; $R^2 = 4\text{-SO}_2\text{Me}$	12	62
22		10	66
23		12	65

[a] The substrate (1 mmol) was treated with **2** (1.1 mmol) in the presence of SDS (10 mol %) at 110 °C (oil-bath) in water (5 mL).
[b] The yield of 1,3-diaryl-2,3-dihydro-1,5-benzothiazepine after chromatographic purification.
[c] The products were characterized by IR, NMR and MS.

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17. *Typical experimental procedure. Representative procedure for the synthesis of the starting 1,3-diarylpropenones. 1-(4-methylsulfanylphenyl)-3-(4-methylphenyl)-prop-2-enone (Table 1, entry 16)*: The starting 1,3-diarylpropenones were prepared following the literature procedure.[9] In a typical experiment 1-(4-methylsulfanylphenyl)-ethanone (0.16 g, 1 mmol, 1 equiv) in EtOH (0.5 mL) was treated with $LiOH{\cdot}H_2O$ (4 mg, 0.1 mmol, 10 mol %) under magnetic stirring for 35 min at rt (~25–30 °C) followed by addition of 4-methylbenzaldehyde (0.12 g, 1 mmol, 1 equiv). The mixture was stirred magnetically until complete consumption of the starting materials (35 min, GCMS). After completion of the reaction, a yellow precipitate was formed and this served as an indicator for monitoring the reaction visually. EtOH was removed under reduced pressure. The residue was diluted with water (5 mL), neutralized with 2% aqueous HCl and extracted with EtOAc (3 × 5 mL). The combined EtOAc extracts were washed with brine solution (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford 1-(4-methylsulfanylphenyl)-3-(4-methylphenyl)-prop-2-enone (0.23 g, 87%). Yellow solid; mp 125–127 °C; IR (KBr): 1652, 1595, 1338, 1224, 1093 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H), 2.56 (s, 3H), 7.22 (d, J = 7.8 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 7.45–7.55 (m, 3H), 7.79 (d, J = 15.6 Hz, 1H), 7.95 (d, J = 8.3 Hz, 2H). MS (EI) m/z: 268 (M^+). Anal. Calcd for $C_{17}H_{16}OS$: C, 76.08; H, 6.01; S, 11.95%. Found: C, 76.10; H, 6.05; S, 11.93%. The remaining diarylpropenones were prepared following this general procedure. The physical data (IR, NMR, MS) of all known compounds were identical with those in the literature.[9a] The physical data (IR, NMR, MS) of a few representative new compounds are provided below. *1-(4-Trifluoro-methylphenyl)3-(4-methylsulfanylphenyl)prop-2-enone (Table 1, entry 17)*: Yellow solid; mp 133–135 °C IR (KBr): 1653, 1596, 1333, 1125, 810 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.53 (s, 3H), 7.25-7.28 (m, 2H), 7.44 (d, J = 15.6 Hz, 1H), 7.56 (d, J = 8.3 Hz, 2H), 7.75-7.81 (m, 3H), 8.09 (d, J = 8.0 Hz, 2H). MS (EI) m/z: 322 (M^+). Anal. Calcd for $C_{17}H_{13}F_3OS$: C, 63.34; H, 4.06; S, 9.95%. Found: C, 63.38; H, 4.10; S, 9.96%. *3-(4-Methanesulfonylphenyl)-1-(4-trifluoromethyl-phenyl)prop-2-enone (Table 1, entry 21)*: An aqueous solution of Oxone® (50% w/v, 3 mmol, 3 equiv) was added dropwise to a stirred solution of 1-(4-trifluoromethylphenyl)-3-(4-methylsulfanylphenyl)prop-2-enone (0.32 g, 1 mmol) in 1,4-dioxane (10 mL) at 0 °C. The reaction was allowed to proceed with stirring at rt (~25–30 °C) for 4 h (TLC). The usual purification afforded a white solid product (0.30 g, 85%); mp. 137-139 °C; IR (KBr): 1668, 1615, 1324, 1146, 971, 826 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ *3.09 (s, 3H), 7.59 (d,* J = 15.7 Hz, 1H), 7.78–7.87 (m, 5H), 8.02 (d, J = 8.3 Hz, 2H), 8.12 (d, J = 8.1 Hz, 2H). MS (EI) m/z: 354 (M^+). Anal. Calcd for $C_{17}H_{13}F_3O_3S$: C, 57.62; H, 3.70; S, 9.05%. Found: C, 57.66; H, 3.71; S, 9.03%. *Procedure for benzothiazepine synthesis. 2,3-Dihydro-2,4-diphenyl-1,5-benzothiazepine* (**3**) *(Table 1, entry 1)*: A mixture of 1 (0.21 g, 1 mmol) in water (5 mL) was heated under reflux (oil-bath temp 110 °C) under magnetic stirring until it formed a melt admixed with water as tiny liquid droplets after which 2 (0.13 g, 1.1 mmol, 1.1 equiv) was added followed by SDS (29 mg, 10 mol %) and the mixture was stirred at 110 °C for 12 h. The cooled (rt) reaction mixture was extracted with EtOAc (3 × 5 mL), the combined EtOAc extracts were washed with brine, dried (Na_2SO_4) and concentrated under rotary vacuum evaporation. The crude product was subjected to column chromatography (silica gel 60-120) using EtOAc/hexane (2:98) as eluent to afford 2,3-dihydro-2,4-diphenyl-1,5-benzothiazepine 3 (0.20 g, 65%) as a yellow solid, identical (spectral data and mp) with an authentic compound.[2j] The remaining reactions were carried out following this general procedure. All the product structures were in full agreement with the spectral data (IR, NMR and MS) and gave satisfactory elemental analyses (where applicable). The physical data (mp, IR, NMR, MS) of a few representative new compounds are provided. *2,3-Dihydro-2-(2-fluorophenyl)-4-(4-chlorophenyl)-1,5-benzothiazepine (Table 1, entry 10)*: Yellow solid; mp 150–152 °C; IR (KBr) ν: 1453, 1481, 1610, 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.93 (t, J = 12.8 Hz, 1H), 3.28 (dd, J = 4.6, 12.9 Hz, 1H), 5.37 (dd, J = 4.6, 12.6 Hz, 1H), 7.02–7.25 (m, 3H), 7.27–7.30 (m, 2H), 7.45–7.56 (m, 4H), 7.66–7.69 (m, 1H), 8.04 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 36.2, 52.6, 115.2, 115.5, 122.5, 124.5, 125.4, 125.7, 127.8, 128.3, 128.7, 129.2, 130.4, 135.1, 135.9, 137.3, 152.3, 156.9, 160.2, 167.5; MS (MALDI-TOF) m/z 368(MH^+). Anal. Calcd for $C_{21}H_{15}ClFNS$: C, 68.56; H, 4.11; N, 3.81; S, 8.72%. Found: C, 68.58; H, 4.13; N, 3.80; S, 8.71%. *2,3-Dihydro-2-(4-methylsulfonylphenyl)-4-(4-trifluoromethylphenyl)-1,5- benzothiazepine (Table 1), entry 21*: Yellow solid; mp 198–200 °C; IR (KBr) ν: 1318, 1617, 1658 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.05–3.13 (m, 4H), 3.31 (dd, J = 4.9, 13.0 Hz, 1H), 5.01 (dd, J = 4.7, 12.5 Hz, 1H), 7.18–7.35 (m, 2H), 7.49–7.52 (m, 3H), 7.60–7.62 (m, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.90 (d, J = 8.2 Hz, 2H), 8.16 (d, J = 8.1 Hz, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 36.1, 43.3, 58.3, 121.4, 122.1, 123.9, 125.1, 125.8, 126.9, 127.2, 128.2, 129.3, 130.6, 131.0, 134.8, 139.8, 140.5, 146.3, 149.1, 151.6, 167.8; MS (MALDI-TOF) m/z 462.7 (MH^+). Anal. Calcd for $C_{23}H_{18}F_3NO_2S_2$: C, 59.86; H, 3.93; N, 3.03; S, 13.90%. Found: C, 59.88; H, 3.96; N, 3.00; S, 13.92%. *7-Phenyl-5,6,6a,7-tetrahydro-8-thia-13-aza-benzo[5,6]cyclohepta[1,2-a]naphthalene (Table 1, entry 23)*: Yellow solid; mp 165–167 °C; IR (KBr) ν: 1449, 1484, 1589, 2920 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.42–1.47 (m, 1H), 1.85–1.94 (m, 1H), 2.68–2.74 (m, 1H), 3.01–3.12 (m, 1H), 3.35–3.39 (m, 1H), 4.78 (d, J = 12.3 Hz, 1H), 7.13–7.58 (m, 12H), 8.51 (d, J = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 24.8, 25.4, 43.3, 61.0, 123.7, 125.5, 125.9, 126.8, 127.4, 127.7, 128.4, 129.4, 130.4, 131.8, 132.5, 135.5, 140.4, 144.0, 152.9, 168.6. MS (EI) m/z 341 (M^+). Anal. Calcd for $C_{23}H_{19}NS$: C, 80.90; H, 5.61; N, 4.10; S, 9.39%. Found: C, 80.92; H, 5.63; N, 4.12; S, 9.38%.
18. (a) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed* **2005**, *44*, 3275–3279; (b) Klijn, J. E.; Engberts, J. B. F. N. *Nature* **2005**, *435*, 746–747.