

Microwave-assisted synthesis of novel aryloxyacetyl hydrazones molecular tweezers under solvent-free conditions

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A rapid, efficient and eco-friendly method for the preparation of new aryl-1,4-bisoxycetylhydrazone molecular tweezers was reported. The reaction is accelerated by microwave irradiation under solvent-free conditions in the presence of solid Al_2O_3 . The structures of these new molecular tweezers were characterised by ^1H NMR, IR, MS spectra and elemental analysis.

Keywords: aryloxyacetyl hydrazones, molecular tweezers, microwave irradiation, solvent-free conditions

The design and synthesis of artificial receptors that carry out molecular recognition using weak non-covalent interactions has become one of the most challenging and attractive fields in modern bioorganic chemistry.^{1–3} Among the various types of artificial receptors which have been developed in recent years, molecular tweezers have attracted attention in molecular recognition, mimics of enzyme catalysis and for the resolution of racemates as well as being used as molecular devices^{4,5} because their natural occurring cavities provide appropriate microenvironment for substrates. Aryloxyhydrazones, which possess inherently rigid structures, are ideal building blocks for the construction of molecular tweezers. The N–H subunits in the hydrazone help to form hydrogen bonds which are considered to be one of the most effective driving forces for molecular recognition. Molecular tweezers with 1,4-diphenoxyacetic acid as a spacer unit and hydrazones as arms have rarely been reported. In order to develop new molecular tweezer artificial receptors and to investigate their recognition ability for neutral molecules, we have designed and synthesised some novel aryloxyhydrazones.

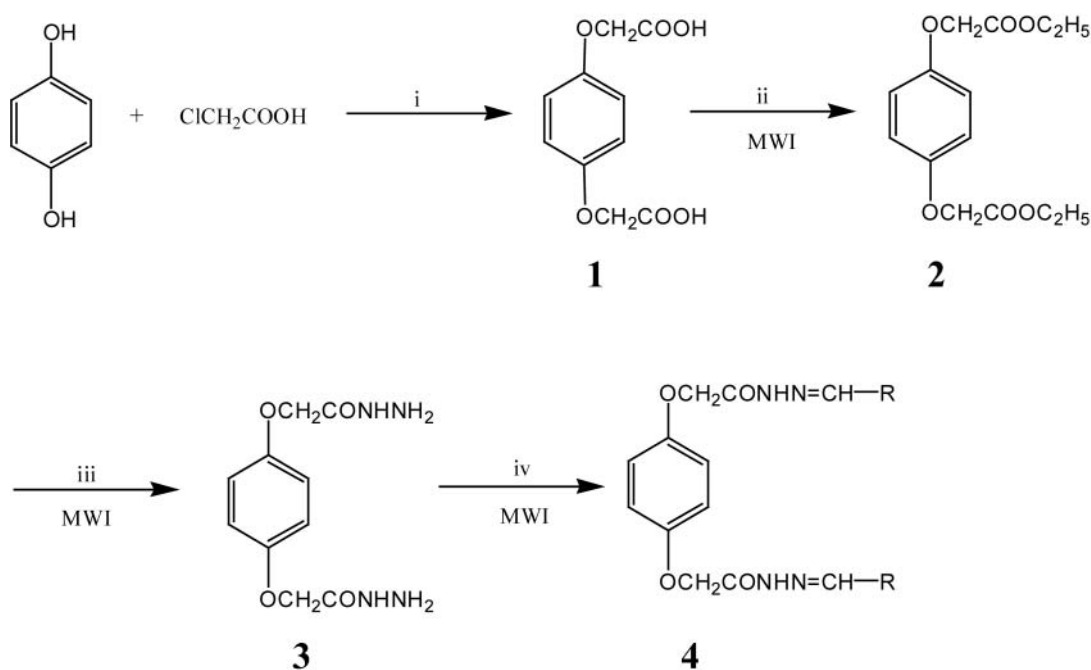
Microwave-assisted organic synthesis has attracted considerable interest and is an important technique in green chemistry. This technology can enhance the chemical yield, ease of manipulation and shorten the reaction time.^{6,7} In continuation

of our ongoing program to synthesise tweezer artificial receptors using microwave activation,^{8–10} we report rapid synthetic method leading to aryloxyhydrazone molecular tweezer artificial receptors. The reaction proceeds in the solid state using microwave radiation and has not been attempted previously. We have made some preliminary investigations of the recognition properties of these molecular tweezers for aromatic amines. The synthetic route is shown in Scheme 1.

Results and discussion

As illustrated in Table 1, the microwave-enhanced solvent-free conditions method compared with the conventional solvent method has the following advantages: (1) the reaction avoids the use of organic solvents, and reduces the pollution of the environment; (2) the reaction rate increased 240–540 times, and reduced the reaction time; and (3) the yields of molecular tweezers have increased. Microwave-assisted solvent-free conditions method provided a simple, safe, fast, efficient and green synthesis method for aryloxyacetyl hydrazones molecular tweezers.

The recognition of molecular tweezers for aromatic amines has been investigated by UV-visible spectra titration in CHCl_3 at 25 °C. Using the nonlinear least squares curve-fitting



Scheme 1 Reagents and conditions: (i) NaOH; (ii) $\text{C}_2\text{H}_5\text{OH}$, 98% H_2SO_4 ; (iii) $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$; (iv) RCHO , Al_2O_3 .

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Table 1 Comparison of the synthesis of molecular tweezers **4a–l** between the solvent-free conditions under microwave irradiation and conventional heating

Product	R	Tradition method		Microwave method		t_c/t_w^a
		Time/min	Yield/%	Time/min	Yield/%	
4a	C ₆ H ₅	1440	35	3	90	480
4b	4-O ₂ NC ₆ H ₄	1800	32	4.5	88	400
4c	3-O ₂ NC ₆ H ₄	1800	34	4	92	450
4d	4-HOC ₆ H ₄	1500	41	3.5	94	428
4e	3-HOC ₆ H ₄	1560	31	3.5	89	446
4f	2-HOC ₆ H ₄	1680	30	4	88	420
4g	4-CH ₃ OC ₆ H ₄	1620	28	4	86	405
4h	4-ClC ₆ H ₄	1440	29	5	86	288
4i	4-BrC ₆ H ₄	1440	31	6	88	240
4j	2-ClC ₆ H ₄	1800	27	6	89	300
4k	4-HO-3-CH ₃ OC ₆ H ₃	1620	40	3	93	540
4l	4-(CH ₃) ₂ NC ₆ H ₄	1440	36	5	90	288

t_c , Tradition method time; t_w , microwave method time.

method, we obtained the association constants for the complex. The preliminary results showed that these molecular tweezers possessed the ability to form complexes with the guest aromatic amines which were examined. The supramolecular complexes consisted of 1:1 host and guest molecules. The association constants of molecular tweezer **4a**, for example, is 1307.54, 2015.52, 2621.93 L · mol⁻¹ for *o*-methoxyaniline, *m*-methoxyaniline, *p*-methoxyaniline respectively. The details of the molecular recognition of these molecular tweezers are under further investigation.

Experimental

Melting points were determined on a micro-melting point apparatus and the thermometer was uncorrected. IR spectra were obtained on 1700 Perkin-Elmer FTIR using KBr disks. ¹H NMR spectra were recorded on a Varian INORA 400MHz spectrometer in DMSO-*d*₆ as solvent and TMS as internal standard. Mass spectra were determined on Finnigan LCQ^{DECA} instrument. Elemental analysis was performed on a Carlo-Erba-1106 auto analyser. Microwave irradiation was carried out with a reliable MCL-3 microwave oven at full power (700 W). This was modified from a domestic microwave oven and tested to conform to the performance index before use. All the solvents were purified before use.

Hydroquinone-1,4-diacetic acid (1): Hydroquinone (0.1 mol), water (50 mL) and sodium hydroxide (0.6 mol) and chloroacetic acid (0.2 mol) were mixed thoroughly in a beaker (150 mL) and heated in water bath for 15 min. After cooling to room temperature, hydrochloric acid was added to the liquid until pH=1. The solid was collected by suction filtration and washed with water. The crude product was recrystallised from hydrochloric acid (1%) to give a pure product. The physical and spectra data of the compound is as follows. White solid, yield 78%, m.p. 256–257 °C (lit.¹¹ 258–260 °C), IR (cm⁻¹): 3225, 2918, 1761, 1710, 1599, 1493, 1432, 1187. ESI-MS *m/z* (%): 249 [(M+23)⁺, 100].

Diethylhydroquinone-1,4-ethyl diacetate (2): Ethanol (30 mL), conc. H₂SO₄ (0.5 mL) and 2.3 g (10 mmol) hydroquinone 1,4-diacetic acid were mixed thoroughly in a round-bottom flask (100 mL). The mixture was then placed in the microwave (350 W) oven and irradiated for 10 min. The reaction mixture was suspended in huge water. The solid was collected by suction filtration. The crude product was recrystallised from ethanol–water to give the pure product as a white solid, yield 90%, m.p. 71–72 °C (lit.¹² 70–71 °C), IR (cm⁻¹): 2984, 1759, 1598, 1493, 1442, 1179. ESI-MS *m/z* (%): 305 [(M+23)⁺, 100].

Hydroquinone-1,4-diacetyl hydrazide (3): Hydroquinone-1,4-ethyl diacetate 1.4 g (5 mmol) and hydrazine hydrate (10 mL) were added to a round-bottom flask (50 mL). The mixture was irradiated (300 W) for 3 min. After cooling, the solid residue was washed with ethanol (5 mL), water (5 mL) and dried to afford a white solid, yield 94%, m.p. 235–236 °C (lit., 238–239 °C)¹³, IR (cm⁻¹): 3315, 3260, 2913, 1684, 1597, 1500, 1437, 1197. ESI-MS *m/z* (%): 227 [(M+23)⁺, 100].

Preparation of molecular tweezers **4a–l**; general procedure

Hydroquinone-1,4-diacetyl hydrazide (0.5 mmol), two drops of acetic acid (catalyst), aromatic aldehyde (1.5 mmol) and 1g neutral solid alumina (10 mmol) were mixed thoroughly in a porcelain mortar. After grinding, the mixture was placed in a 25 mL beaker, and the beaker was placed in the microwave (300 W) oven and irradiated for 3–6 min. The reaction was monitored by TLC until it was completed. The mixture was extracted with DMF (5 mL × 3). The solvent was evaporated to give the crude products. The crude product was recrystallised from DMF–water to give the pure products. The physical and spectroscopic data of the compounds **4a–l** are as follows.

***N,N'*-benzylidene-2,2'-[1,4-phenylenebis(oxy)]diacetylhydrazone [molecular tweezer (4a)]**: White solid, yield 90%, m.p. 221–222 °C. IR (cm⁻¹): 3191, 3062, 2790, 1683, 1507, 1411, 1291, 754; ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.56 (d, *J* = 13.2 Hz, 2H, NH), 8.35 (s, 1H, NCH), 8.00 (s, 1H, NCH), 7.70 (d, *J* = 4.8 Hz, 4H, ArH), 7.45–7.43 (m, 6H, ArH), 6.97–6.87 (m, 4H, ArH), 5.08 (s, 2H, OCH₂), 4.61 (s, 2H, OCH₂). ESI-MS *m/z* (%): 883 [(2M+23)⁺, 100]. Anal. Calcd for C₂₄H₂₂N₄O₄: C, 66.97; H, 5.15; N, 13.02. Found: C, 66.99; H, 5.12; N, 12.99%.

***N,N'*-[4-(nitro)benzylidene]-2,2'-[1,4-phenylenebis(oxy)]diacetylhydrazone [molecular tweezer (4b)]**: Pale yellow solid, yield 88%, m.p. 245–246 °C. IR (cm⁻¹): 3191, 3077, 2764, 1682, 1586, 1511, 1324, 1209, 754; ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.87 (s, 2H, NH), 8.45 (s, 1H, NCH), 8.31–8.26 (m, 4H, ArH), 8.10 (s, 1H, NCH), 7.99–7.95 (m, 4H, ArH), 6.98–6.89 (m, 4H, ArH), 5.12 (s, 2H, OCH₂), 4.65 (s, 2H, OCH₂). ESI-MS *m/z* (%): 519 [(M-1)⁻, 100]. Anal. Calcd for C₂₄H₂₀N₆O₈: C, 55.39; H, 3.87; N, 16.15. Found: C, 55.33; H, 3.85; N, 16.18%.

***N,N'*-[3-(nitro)benzylidene]-2,2'-[1,4-phenylenebis(oxy)]diacetylhydrazone [molecular tweezer (4c)]**: Pale yellow solid, yield 92%, m.p. 269–270 °C. IR (cm⁻¹): 3199, 3077, 2968, 1692, 1614, 1508, 1349, 1208, 832; ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.82 (s, 2H, NH), 8.52–8.47 (m, 2H, NCH), 8.27–8.11 (m, 6H, ArH), 7.77–7.71 (m, 2H, ArH), 6.98–6.89 (m, 4H, ArH), 5.13 (s, 2H, OCH₂), 4.64 (s, 2H, OCH₂). ESI-MS *m/z* (%): 1063[(2M+23)⁺, 100]. Anal. Calcd for C₂₄H₂₀N₆O₈: C, 55.39; H, 3.87; N, 16.15. Found: C, 55.30; H, 3.89; N, 16.17%.

***N,N'*-[4-(hydroxyl)benzylidene]-2,2'-[1,4-phenylenebis(oxy)]diacetylhydrazone [molecular tweezer (4d)]**: White solid, yield 94%, m.p. 297–298 °C. IR (cm⁻¹): 3473, 3343, 3077, 2926, 1680, 1606, 1509, 1439, 1224, 829; ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.34 (d, *J* = 16.4 Hz, 2H, NH), 9.92 (s, 2H, OH), 8.22 (s, 1H, NCH), 7.89 (s, 1H, NCH), 7.52 (d, *J* = 8.4 Hz, 4H, ArH), 6.96–6.80 (m, 8H, ArH), 5.02 (s, 2H, OCH₂), 4.56 (s, 2H, OCH₂). ESI-MS *m/z* (%): 947 [(2M+23)⁺, 100]. Anal. Calcd for C₂₄H₂₂N₄O₆: C, 62.33; H, 4.79; N, 12.12. Found: C, 62.20; H, 4.71; N, 12.15%.

***N,N'*-[3-(hydroxyl)benzylidene]-2,2'-[1,4-phenylenebis(oxy)]diacetylhydrazone [molecular tweezer (4e)]**: White solid, yield 89%, m.p. 246–247 °C. IR (cm⁻¹): 3342, 3174, 3046, 2897, 1683, 1595, 1506, 1438, 1225, 831; ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.50 (d, *J* = 12.4 Hz, 2H, NH), 9.61 (d, *J* = 9.2 Hz, 2H, OH), 8.24 (s, 1H, NCH), 7.91 (s, 1H, NCH), 7.26–6.81 (m, 12H, ArH), 5.05 (s, 2H, OCH₂), 4.59 (s, 2H, OCH₂). ESI-MS *m/z* (%): 947 [(2M+23)⁺, 100]. Anal. Calcd for C₂₄H₂₂N₄O₆: C, 62.33; H, 4.79; N, 12.12. Found: C, 62.19; H 4.84; N, 12.14%.

***N,N'*-[2-(hydroxyl)benzylidene]-2,2'-[1,4-phenylenebis(oxy)]diacetylhydrazone [molecular tweezer (4f)]**: Pale yellow solid, yield 88%, m.p. 240–241 °C. IR (cm⁻¹): 3442, 3189, 3086, 2923, 1679, 1507, 1411, 1213, 760; ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.79 (s, 1H, NH), 11.51 (s, 1H, NH), 11.07 (s, 1H, OH), 10.05 (s, 1H, OH), 8.56 (s, 1H, NCH), 8.30 (s, 1H, NCH), 7.70 (d, *J* = 8 Hz, 1H, ArH), 7.52 (d, *J* = 8 Hz, 1H, ArH), 7.32–7.22 (m, 1H, ArH), 6.99–6.83 (m, 10H, ArH), 5.04 (s, 2H, OCH₂), 4.63 (s, 2H, OCH₂). ESI-MS *m/z* (%): 463 [(M+1)⁺, 100]. Anal. Calcd for C₂₄H₂₂N₄O₆: C, 62.33; H, 4.79; N, 12.12. Found: C, 62.37; H, 4.66; N, 12.08%.

***N,N'*-[4-(methoxy)benzylidene]-2,2'-[1,4-phenylenebis(oxy)]diacetylhydrazone [molecular tweezer (4g)]**: White solid, yield 86%, m.p. 241–242 °C. IR (cm⁻¹): 3191, 3096, 2966, 2837, 1680, 1608, 1508, 1252, 827; ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.43 (d, *J* = 16.8 Hz, 2H, NH), 8.28 (s, 1H, NCH), 7.94 (s, 1H, NCH), 7.64 (d, *J* = 7.2 Hz, 4H, ArH), 7.02–6.86 (m, 8H, ArH), 5.04 (s, 2H, OCH₂), 4.57 (s, 2H, OCH₂), 3.80 (s, 6H, OCH₃). ESI-MS *m/z* (%): 1003[(2M+23)⁺, 100]. Anal. Calcd for C₂₆H₂₆N₄O₆: C, 63.66; H, 5.34; N, 11.42. Found: C, 63.71; H, 5.38; N, 11.38%.

N,N'-[4-(chloro)benzylidene]-2,2'-[1,4-phenylenebis(oxy)]diacetohydrazone [molecular tweezer (**4h**): White solid, yield 86%, m.p. 255–255 °C. IR (cm⁻¹): 3190, 3096, 2971, 2926, 1681, 1508, 1409, 1208, 820. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.63 (s, 2H, NH), 8.33 (s, 1H, NCH), 7.99 (s, 1H, NCH), 7.74–7.71 (m, 4H, ArH), 7.52–7.49 (m, 4H, ArH), 6.96–6.87 (m, 4H, ArH), 5.07 (s, 2H, OCH₂), 4.60 (s, 2H, OCH₂). ESI-MS *m/z* (%): 499 (M⁺, 100). Anal. Calcd for C₂₄H₂₀Cl₂N₄O₄: C, 57.73; H, 4.04; N, 11.22. Found: C, 57.74; H, 4.02; N, 11.25.

N,N'-[4-(bromo)benzylidene]-2,2'-[1,4-phenylenebis(oxy)]diacetohydrazone [molecular tweezer (**4i**): White solid, yield 88%, m.p. 272–273 °C. IR (cm⁻¹): 3183, 3090, 2966, 1684, 1509, 1408, 1210, 1091, 820. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.63 (s, 2H, NH), 8.32 (d, *J* = 2.4 Hz, 1H, NCH), 7.97 (s, 1H, NCH), 7.67–7.63 (m, 8H, ArH), 6.96–6.86 (m, 4H, ArH), 5.07 (s, 2H, OCH₂), 4.60 (s, 2H, OCH₂). ESI-MS *m/z* (%): 1175[(2M-1)⁺, 100]. Anal. Calcd for C₂₄H₂₀Br₂N₄O₄: C, 49.00; H, 3.43; N, 9.52. Found: C, 49.02; H, 3.41; N, 9.55%.

N,N'-[2-(chloro)benzylidene]-2,2'-[1,4-phenylenebis(oxy)]diacetohydrazone(molecular tweezer (**4j**): White solid, yield 89%, m.p. 263–264 °C. IR (cm⁻¹): 3197, 3107, 2988, 2866, 1699, 1506, 1428, 1224, 1088, 753. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.78 (s, *J* = 26 Hz, 2H, NH), 8.76 (s, 1H, NCH), 8.39 (s, 1H, NCH), 8.02–7.96 (m, 2H, ArH), 7.54–7.39 (m, 6H, ArH), 6.99–6.83 (m, 4H, ArH), 5.09 (s, 2H, OCH₂), 4.62 (s, 2H, OCH₂). ESI-MS *m/z* (%): 1021[(2M+23)⁺, 40]. Anal. Calcd for C₂₄H₂₀Cl₂N₄O₄: C, 57.73; H, 4.04; N, 11.22. Found: C, 57.71; H, 4.00; N, 11.16%.

N,N'-[4-(hydroxyl)-3-(methoxy)benzylidene]-2,2'-[1,4-phenylenebis(oxy)]diacetohydrazone [molecular tweezer (**4k**): White solid, yield 93%, m.p. 247–248 °C. IR (cm⁻¹): 3339, 3245, 3054, 2099, 1688, 1604, 1505, 1441, 1221, 1068, 817. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.37 (d, *J* = 13.2 Hz, 2H, NH), 9.52 (d, *J* = 21.6 Hz, 2H, OH), 8.21 (s, 1H, NCH), 7.88 (s, 1H, NCH), 7.26 (s, 2H, ArH), 7.09–7.04 (m, 2H, ArH), 6.96–6.80 (m, 6H, ArH), 5.05 (s, 2H, OCH₂), 4.56 (s, 2H, OCH₂), 3.80 (s, 6H, OCH₃). ESI-MS *m/z* (%): 523 [(M+1)⁺, 37]. Anal. Calcd for C₂₆H₂₆N₄O₈: C, 59.77; H, 5.02; N, 10.72. Found: C, 59.87; H 5.10; N, 10.68%.

N,N'-[4-bis(methyl)aminobenzylidene]-2,2'-[1,4-phenylenebis(oxy)]diacetohydrazone [molecular tweezer (**4l**): Pale yellow solid, yield 90%, m.p. 273–274 °C. IR (cm⁻¹): 3536, 3188, 3099, 2982, 1680, 1509, 1413, 1280, 1212, 1085, 819, 777. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.28 (s, 1H, NH), 11.21 (s, 1H, NH), 8.18 (s, 1H, NCH), 7.86 (s, 1H, NCH), 7.49 (d, *J* = 8.4 Hz, 4H, ArH), 6.96–6.85 (m, 4H, ArH),

6.75–6.71 (m, 4H, ArH), 5.01 (s, 2H, OCH₂), 4.54 (s, 2H, OCH₂), 2.97–2.96 (m, 12H, N(CH₃)₂). ESI-MS *m/z* (%): 1055 [(2M+23)⁺, 100]. Anal. Calcd for C₂₈H₃₂N₆O₄: C, 65.10; H, 6.24; N, 16.27. Found: C, 65.14, H 6.27; N, 16.30%.

Preparation of **4a-l**; conventional method

Hydroquinone 1,4-diacetyl hydrazine (0.5 mmol), three drops of acetic acid (catalyst), aromatic aldehyde (1.5 mmol) and DMF (10 mL) were added to a round-bottom flask (25 mL). The mixture was heated at 85 °C for 24–30 h. After cooling to room temperature, water was added to precipitated solid. The precipitated product was filtered and washed with water. The crude material was recrystallised from DMF–water to afford the pure products. The yields are indicated in Table 1.

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