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Traceless Solid-Phase Synthesis of Substituted Xanthines

Rongjun He, Shi Min Ching, and Yulin Lam*

Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543

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A traceless solid-phase route to substituted xanthines, based on the late-stage pyrimidine ring closure, has been developed. This method is especially useful for the preparation of xanthines containing a variety of substituents at the N1, N3, N7, and C8 positions in an unambiguous manner. A representative set of 22 compounds was prepared.

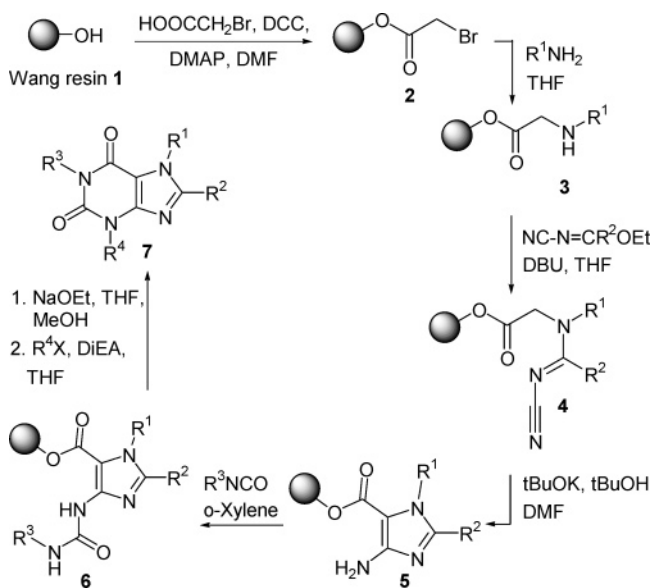
Introduction

Xanthines constitute an important class of pharmacologically active compounds which are commonly used for their effects as mild stimulants, bronchodilators, phosphodiesterase inhibitors, CFTR chloride-channel activators, and adenosine-receptor antagonists.¹ In recent years, the spectrum of clinical applications of xanthines has continued to widen and presently include their use as anticonvulsants,² nootropics,³ and therapeutics for the treatment of migraine and illnesses where underactivation of the HM74A receptor contributes to the disease.⁴ Accordingly, methodologies for the preparation of xanthines have attracted much attention, and various solution-phase syntheses of these compounds have been reported.⁵ Generally, these syntheses involve multistep reactions and require tedious chromatographic separations which would limit the synthesis of large number of compounds. A solid-phase approach to the synthesis of small organic molecule libraries⁶ would offer a good pathway toward a large number of these analogues. We have recently reported a traceless solid-phase synthesis of xanthines using the PS-MB-CHO resin.⁷ Although the reaction is highly efficient, the strategy is limited to the preparation of mono- and disubstituted xanthines. As part of our continuing studies on the solid-phase synthesis of purines, we herein present the results of a new synthetic procedure for the preparation of disubstituted, trisubstituted, or fully substituted xanthines (Scheme 1).

Results and Discussion

Solution-Phase Synthesis. Prior to the solid-phase synthesis, preliminary solution-phase studies (Scheme 2) were carried out to survey the requisite reaction conditions and establish the optimizations required for solid-phase format. To begin our investigation, we had to prepare *N*-substituted glycine benzyl ester **10** which was initially achieved by coupling benzyl alcohol **8** with Fmoc-glycine followed by Fmoc-deprotection and alkylation. However, further experimentation showed that **10** could be obtained more expedi-

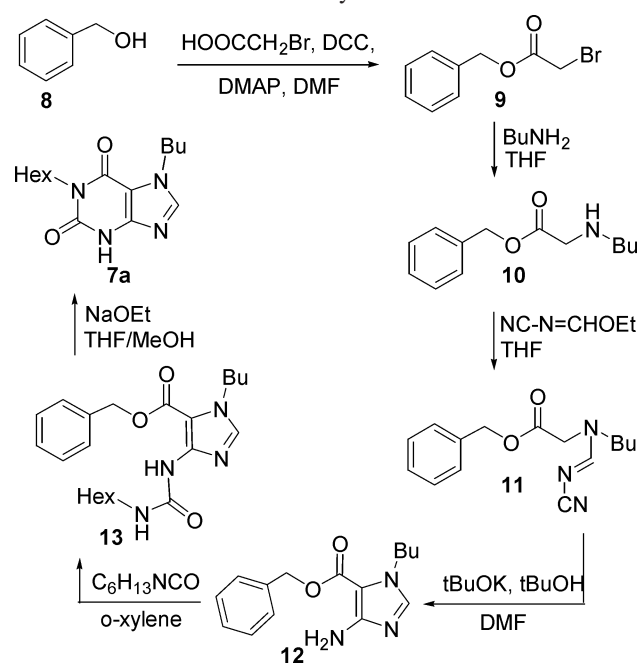
Scheme 1. SPOS of Xanthines



ently and in better yields by reacting **8** with bromoacetic acid to give **9** which, in turn, could be efficiently treated with butylamine in THF to provide **10** in a 75% overall yield. It is interesting to note that the latter reaction is dependent on the concentration of the amine with lower concentrations giving better yields of **10**. Hence, it was necessary to keep the concentration of the amine below 0.2 M for good yields.

Treatment of **10** with ethoxymethylene cyanamide gave intermediate **11** which upon reaction with NaOEt in anhydrous EtOH underwent rapid imidazole ring formation.⁸ However ¹H NMR data of the product obtained showed that the benzyl group had been replaced by an ethyl moiety which meant that the procedure could not be applied on solid-phase format. Attempts to lower the reaction temperature to 0 °C did not prevent the loss of the benzyl moiety, and at -30 °C, the cyclization reaction ceased to proceed. To effect the formation of **12**, we eventually replaced NaOEt/EtOH with tBuOK/tBuOH which also provided a rapid imidazole ring formation but without displacement of the benzyl group. With **12** in hand, we proceeded to treat it with hexyl isocyanate

* To whom correspondence should be addressed. E-mail: chmlamyl@nus.edu.sg. Fax: (65)-6779-1691.

Scheme 2. Solution-Phase Study

which provided **13** in a 90% yield. Subsequent ring closure of **13** with NaOEt in a MeOH–THF mixture afforded **7a** in good yield.

Solid-Phase Synthesis. With the solution-phase pathway established, we proceeded to prove the versatility of this methodology for solid-phase synthesis. Wang resin **1** in DCC/DMAP/DMF was allowed to react with bromoacetic acid at room temperature. The formation of **2** was amenable to KBr FTIR monitoring (i.e., disappearance of the OH stretch at 3566 cm^{-1} and the appearance of a strong C=O stretch at 1744 cm^{-1}). Resin **2** was then treated with various primary amines in THF to give **3** which was subsequently reacted with ethoxymethylene cyanamide or methyl ethoxymethylene cyanamide in the presence of DBU to provide resin **4**. Because of the poor swelling ability of polystyrene/1% divinylbenzene in butanol, the cyclization of **4** using tBuOK was carried out in a DMF–tBuOH (v/v 1:1) mixture. The disappearance of the CN stretch at 2178 cm^{-1} and the shift of the C=O stretch from 1744 to 1690 cm^{-1} were indicative of the formation of **5**. Treatment of **5** with various isocyanates in *o*-xylene ($120\text{--}125\text{ }^\circ\text{C}$, 24 h) provided **6** which underwent a concomitant cyclization-cleavage in NaOEt in MeOH–THF (v/v 1:2) to give 1,7- or 1,7,8-substituted xanthines which was subsequently alkylated in a one-pot reaction to afford the fully substituted xanthines. To illustrate the versatility of this chemistry, a representative set of 22 compounds (**7a–7v**) was prepared (Figure 1). The overall yields obtained were 14–35% (purities of >95% by NMR) indicating an average yield of $\geq 75\%$ for each step of the solid-phase reaction, except in the more sterically hindered **7u** and **7v** where lower yields were obtained.

In summary, an efficient and scalable synthetic procedure affording disubstituted, trisubstituted, or fully substituted xanthines in good overall yields has been developed. Further studies are currently in progress to extend this methodology to other purine systems.

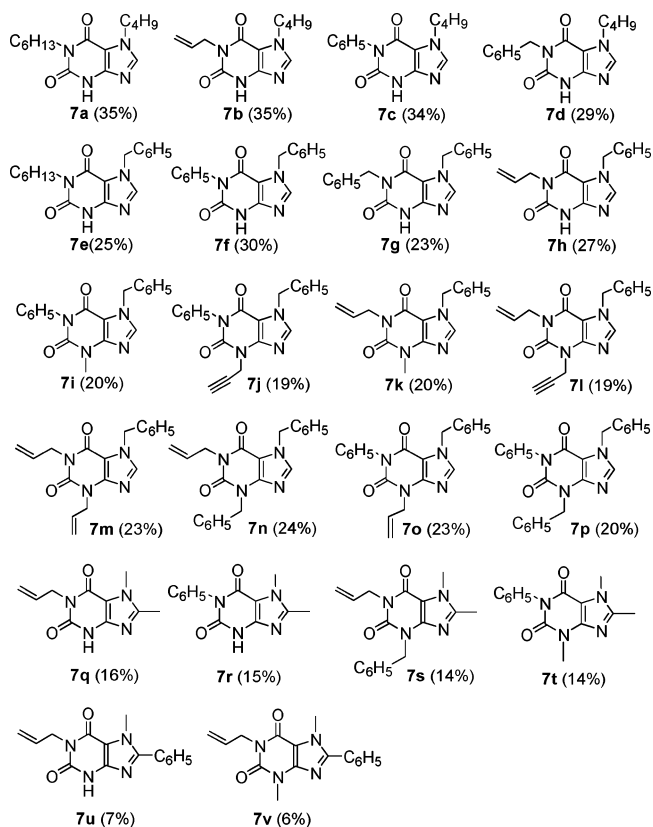


Figure 1. Library of **7**.

Experimental Section

General Procedures. Wang resin was purchased from Tianjin Nankai Hecheng Science and Technology Co. (100–200 mesh, 1.4 mmol/g, 1% divinylbenzene cross-linking). All other chemical reagents were obtained from Aldrich, Merck, Lancaster, or Fluka and were used without further purification. The solid-phase reactions were agitated on a flask shaker SF1 (Stuart Scientific). Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and visualized with UV light or stained with ninhydrin. Flash column chromatograph was performed with silica (Merck, 70–230 mesh).

^1H NMR and ^{13}C NMR spectra were measured at 298 K on a Bruker DPX 300 or DPX 500 Fourier Transform spectrometer. Chemical shifts were reported in parts per million (δ), relative to the internal standard of tetramethylsilane (TMS). The signals observed were described as follows: s (singlet), d (doublet), t (triplet), m (multiplet). The number of protons (n) for a given resonance was indicated as $n\text{H}$. All infrared (IR) spectra were recorded on a Bio-Rad FTS 165 spectrometer. Mass spectra were performed on VG Micromass 7035 spectrometer under electron impact (EI).

Synthesis of Benzyl Bromoacetate (9). Bromoacetic acid (0.5131 g, 3.698 mmol), DCC (0.7630 g, 3.698 mmol), and DMAP (0.0677 g, 0.5547 mmol) were added to benzyl alcohol **8** (0.2000 g, 1.849 mmol) in DMF (5 mL) in the stated order. The reaction mixture was stirred at room temperature for 2 h, then quenched with water (50 mL), and extracted with EtOAc (50 mL \times 3). The combined organic layer was dried with MgSO_4 , filtered, concentrated, and

purified by column chromatography (EtOAc–hexane = 1:20) to give **9** as a pale yellow liquid (0.4201 g, 99% yield). ^1H NMR (CDCl_3 , 300 MHz): δ 7.41–7.36 (m, ArH, 5H), 5.21 (s, ArCH₂, 2H), 3.87 (s, CH₂Br, 2H). ^{13}C NMR (CDCl_3 , 300 MHz): δ 166.8, 134.8, 128.4, 128.4, 128.2, 67.7, 25.7. Mass spectrum (EI): m/z 227.8 (M⁺). Exact mass calcd for C₉H₉BrO₂: m/z 227.9786. Found: 227.9790.

Synthesis of Butylaminoacetic Acid Benzyl Ester (10). Compound **9** (0.5031 g, 2.20 mmol) was dissolved in THF (25 mL), and the solution was cooled in an ice–water bath. Butylamine (0.3213 g, 4.40 mmol) was diluted in THF (25 mL), and the solution was added to **9** dropwise. After which, the ice–water bath was removed, and the reaction mixture was stirred at room temperature for 2 h. This mixture was concentrated and purified by column chromatography (EtOAc–hexane = 1:3 and then MeOH–DCM = 1:20) to get **10** as a colorless liquid (0.3702 g, 76% yield). ^1H NMR (CDCl_3 , 300 MHz): δ 7.35 (s, ArH, 5H), 5.16 (s, ArCH₂, 2H), 3.45 (s, COCH₂NH, 2H), 2.62–2.57 (t, J = 7.0 Hz, NHCH₂CH₂CH₂CH₃, 2H), 1.99 (s, NH, 1H), 1.52–1.42 (m, NHCH₂CH₂CH₂CH₃, 2H), 1.40–1.28 (m, NHCH₂CH₂CH₂CH₃, 2H), 0.93–0.88 (t, J = 7.1 Hz, NHCH₂CH₂CH₂CH₃, 3H). ^{13}C NMR (CDCl_3 , 500 MHz): δ 172.3, 135.5, 128.4, 128.2, 128.2, 66.3, 50.8, 49.1, 32.0, 20.2, 13.8. Mass spectrum (EI): m/z 221.1 (M⁺). Exact mass calcd for C₁₃H₁₉NO₂: m/z 221.1416. Found: 221.1408.

Synthesis of Benzyl N-Methylene Cyanamide Butylcarbamate (11). Compound **10** (0.1362 g, 0.6155 mmol) in THF (3 mL) was cooled in an ice–water bath, and ethoxymethylene cyanamide (0.1207 g, 1.231 mmol) in THF (3 mL) was added dropwise. The reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated and purified by column chromatography (EtOAc–hexane = 1:1) to obtain **11** as a colorless liquid (0.1649 g, 98% yield). ^1H NMR (CDCl_3 , 300 MHz): δ 8.13 (s, CH, 1H), 7.37–7.32 (m, ArH, 5H), 5.17 (s, ArCH₂, 2H), 4.14 (s, COCH₂N, 2H), 3.39–3.34 (t, J = 7.3 Hz, NCH₂CH₂CH₂CH₃, 2H), 1.60–1.50 (m, NCH₂CH₂CH₂CH₃, 2H), 1.36–1.24 (m, NCH₂CH₂CH₂CH₃, 2H), 0.93–0.89 (t, J = 7.4 Hz, CH₂CH₂CH₂CH₃, 3H). ^{13}C NMR (CDCl_3 , 300 MHz): δ 166.6, 163.9, 134.6, 128.3, 128.2, 127.9, 117.5, 67.1, 52.8, 46.7, 29.6, 19.1, 13.2. Mass spectrum (EI): m/z 273.0 (M⁺). Exact mass calcd for C₁₅H₁₉N₃O₂: m/z 273.1477. Found: 273.1475.

Synthesis of 5-Amino-3-butyl-3H-imidazole-4-carboxylic Acid Benzyl Ester (12). tBuOH (5 mL) and tBuOK (0.0616 g, 1.0976 mmol) were added to **11** (0.1500 g, 0.5488 mmol) in THF (5 mL), and the reaction mixture was stirred for 1 h. After which, the reaction mixture was quenched with NH₄Cl, diluted with H₂O (30 mL), and extracted with CH₂Cl₂ (30 mL × 3). The combined organic layer was dried with MgSO₄, filtered, concentrated, and purified by column chromatography (EtOAc–CH₂Cl₂ = 2:1) to give a colorless solid **12** (0.0757 g, 52% yield). ^1H NMR (CDCl_3 , 300 MHz): δ 7.33–7.21 (m, ArH, 5H), 7.09 (s, CH, 1H), 5.20 (s, ArCH₂, 2H), 4.70 (s, NH₂, 2H), 4.00–3.95 (t, J = 7.1 Hz, NCH₂CH₂CH₂CH₃, 2H), 1.63–1.53 (m, NCH₂CH₂CH₂CH₃, 2H), 1.20–1.08 (m, NCH₂CH₂CH₂CH₃, 2H), 0.80–0.76 (t, J = 7.3 Hz, NCH₂CH₂CH₂CH₃, 3H). ^{13}C NMR (CDCl_3 , 300 MHz): δ 160.5, 155.8, 138.8, 136.0, 128.5,

128.1, 128.1, 101.1, 65.4, 47.2, 32.7, 19.4, 13.4. Mass spectrum (EI): m/z 273.1 (M⁺). Exact mass calcd for C₁₅H₁₉N₃O₂: m/z 273.1477. Found: 273.1473.

Synthesis of 3-Butyl-5-(3-hexyl-ureido)-3H-imidazole-4-carboxylic Acid Benzyl Ester (13). Hexyl isocyanate (0.1895 g, 1.49 mmol) was added to a solution of **12** (0.0814 g, 0.298 mmol) in *o*-xylene (7 mL), and the reaction mixture was heated at 120 °C for 8 h. After which, the resulting mixture was concentrated and purified by column chromatography (EtOAc–hexane = 1:3 and then EtOAc–hexane = 1:1) to give **13** (0.1133 g, 90% yield) as a white solid. ^1H NMR (CDCl_3 , 300 MHz): δ 8.66 (s, C₆H₁₃NHCONH, 1H), 8.04 (s, C₆H₁₃NHCONH, 1H), 7.43–7.28 (m, CH and ArH, 6H), 5.34 (s, ArCH₂, 2H), 4.17–4.12 (t, J = 7.1 Hz, NCH₂CH₂CH₂CH₃, 2H), 3.35–3.28 (q, J = 6.5 Hz, NHCH₂CH₂CH₂CH₂CH₂CH₃, 2H), 1.73–1.52 (m, NHCH₂CH₂CH₂CH₂CH₂CH₃ and NCH₂CH₂CH₂CH₃, 4H), 1.31–1.17 (m, NHCH₂CH₂CH₂CH₂CH₂CH₃ and NCH₂CH₂CH₂CH₃, 8H), 0.90–0.85 (m, NHCH₂CH₂CH₂CH₂CH₂CH₃ and NCH₂CH₂CH₂CH₃, 6H). ^{13}C NMR (CDCl_3 , 300 MHz): δ 159.7, 154.6, 148.5, 137.2, 135.4, 128.8, 128.6, 128.5, 103.1, 66.3, 47.8, 40.1, 32.9, 31.5, 29.9, 26.7, 22.5, 19.6, 14.0, 13.5. Mass spectrum (EI): m/z 400.1 (M⁺). Exact mass calcd for C₂₂H₃₂N₄O₃: m/z 400.2474. Found: 400.2471.

Synthesis of 1-Hexyl-7-butylxanthine (7a). THF (6 mL) and MeOH (3 mL), followed by NaOEt (21% (w/w) in denatured EtOH, 0.32 mL, 0.849 mmol) were added to **13** (0.1133 g, 0.283 mmol). The mixture was refluxed at 90 °C for 1 h. Subsequently, the mixture was concentrated, and water (10 mL) was added. The precipitate that formed was removed by filtration. HCl acid (1.5 M) was added dropwise to the filtrate until the pH was <6, and the precipitate that formed was collected and washed with cold water to give **7a** as a white solid (0.0744 g, 90% yield). ^1H NMR (acetone-*d*₆, 300 MHz): δ 10.83 (s, NH, 1H), 7.87 (s, CH, 1H), 4.35–4.30 (t, J = 7.1 Hz, NCH₂CH₂CH₂CH₂CH₂CH₃, 2H), 3.94–3.89 (t, J = 7.5 Hz, NCH₂CH₂CH₂CH₃, 2H), 1.89–1.80 (m, NCH₂CH₂CH₂CH₂CH₂CH₃, 2H), 1.63–1.58 (m, NCH₂CH₂CH₂CH₂CH₃, 2H), 1.43–1.29 (m, NCH₂CH₂CH₂CH₂CH₂CH₃ and NCH₂CH₂CH₂CH₃, 8H), 0.95–0.86 (m, CH₂CH₂CH₂CH₂CH₂CH₃ and CH₂CH₂CH₂CH₃, 6H). ^{13}C NMR (CDCl_3 , 300 MHz): δ 156.8, 152.5, 149.3, 143.6, 108.0, 47.7, 41.5, 34.3, 32.9, 29.4, 28.0, 23.9, 20.8, 14.9, 14.5. Mass spectrum (EI): m/z 292.2 (M⁺). Exact mass calcd for C₁₅H₂₄N₄O₂: m/z 292.1899. Found: 292.1901.

General Procedure for the Preparation of Benzyl Bromoacetate Resin (2). Wang Resin (**1**) (2 g, 2.8 mmol) was swollen in DMF (15 mL) for 30 min. Bromoacetic acid (0.7781 g, 5.6 mmol), DCC (1.1554 g, 5.6 mmol), and DMAP (0.103 g, 0.84 mmol) were added in the stated order. The reaction mixture was shaken at room temperature for 5 h. After which, the resin was filtered, washed with DMF (20 mL × 3), H₂O (20 mL × 3), EtOH (20 mL × 3), CH₂Cl₂ (20 mL × 3), and Et₂O (20 mL × 3), and dried in a vacuum oven at 50 °C for 12 h.

General Procedure for the Preparation of N-Substituted Benzyl Carbamate Resin (3). Resin **2** (2.8516 g, 2.8 mmol) was swollen in THF (30 mL) for 30 min and then cooled in an ice–water bath. The respective primary amine

(3 equiv), diluted in THF (25 mL), was added dropwise. After which, the water bath was removed, and the reaction mixture was shaken at room temperature for 12 h. The resin was then filtered, washed with DMF (20 mL \times 3), H₂O (20 mL \times 3), EtOH (20 mL \times 3), CH₂Cl₂ (20 mL \times 3), and Et₂O (20 mL \times 3), and dried in a vacuum oven at 50 °C for 12 h.

General Procedure for the Preparation of Benzyl *N*-Methylenecyanamide *N*-Substituted Carbamate Resin (4) (R² = H). Resin 3 (2.2698 g, 2.8 mmol) was swollen in THF (15 mL) for 30 min and then cooled in an ice–water bath. Ethoxymethylene cyanamide (0.8236 g, 8.4 mmol) in THF (15 mL) was added dropwise, and the reaction mixture was shaken at room temperature for 12 h. After which, the resin was filtered, washed with DMF (20 mL \times 3), H₂O (20 mL \times 3), EtOH (20 mL \times 3), CH₂Cl₂ (20 mL \times 3), and Et₂O (20 mL \times 3) and dried in a vacuum oven at 50 °C for 12 h.

General Procedure for the Preparation of Benzyl *N*-Methyl Methylene Cyanamide *N*-Substituted Carbamate Resin (4) (R² = CH₃). Resin 3 (2.2551 g, 2.8 mmol) was swollen in THF (20 mL) for 30 min and then cooled in an ice–water bath. DBU (1.066 g, 14 mmol) was added, followed by the dropwise addition of methyl ethoxymethylene cyanamide (0.4704 g, 8.4 mmol) in THF (15 mL). After which, the reaction mixture was shaken at room temperature for 12 h. The resin was then filtered, washed with DMF (20 mL \times 3), H₂O (20 mL \times 3), EtOH (20 mL \times 3), CH₂Cl₂ (20 mL \times 3), and Et₂O (20 mL \times 3), and dried in a vacuum oven at 50 °C for 12 h.

General Procedure for the Preparation of 5-Amino-(3-substituted)imidazole-4-carboxylic Acid Benzyl Ester Resin (5). Resin 4 (2.2876 g, 2.8 mmol) was swollen in DMF (15 mL) for 30 min and then cooled in an ice–water bath. tBuOK (0.6284 g, 5.6 mmol) in tBuOH (15 mL) was added, and the reaction mixture was stirred at room temperature for 2 h. After which, the reaction mixture was quenched with NH₄Cl, and the resin was filtered, washed with DMF (20 mL \times 3), H₂O (20 mL \times 3), EtOH (20 mL \times 3), CH₂Cl₂ (20 mL \times 3), and Et₂O (20 mL \times 3), and dried in a vacuum oven at 50 °C for 12 h.

General Procedure for the Preparation of 5-(3-Substituted Ureido)imidazole-4-carboxylic Acid Benzyl Ester Resin (6). Resin 5 (0.3054 g, 0.3756 mmol) was swollen in *o*-xylene (10 mL) for 30 min. Isocyanate (3 equiv) was added, and the reaction mixture was heated at 120–125 °C for 24 h. The resin was filtered, washed with DMF (20 mL \times 3), H₂O (20 mL \times 3), EtOH (20 mL \times 3), CH₂Cl₂ (20 mL \times 3), and Et₂O (20 mL \times 3), and dried in a vacuum oven at 50 °C for 12 h.

General Procedure for the Preparation of 1,7- or 1,7,8-Substituted Xanthines (7). THF (6 mL), MeOH (3 mL), and NaOEt (21% (w/w) in denatured EtOH, 0.42 mL, 1.1268 mmol) were added to resin 6 (0.3249 g, 0.3756 mmol), and the reaction mixture was refluxed at 90 °C for 2 h. After which, the reaction mixture was filtered, and the resin was washed with MeOH (10 mL \times 3) and CH₂Cl₂ (10 mL \times 3). The combined organic layer was concentrated and purified

by column chromatography (EtOAc–hexane = 2:1 and then MeOH–CH₂Cl₂ = 1:10) to give 7.

General Procedure for the Preparation of 1,3,7- or 1,3,7,8-Substituted Xanthines (7). THF (6 mL), MeOH (3 mL), and NaOEt (21% (w/w) in denatured EtOH, 0.42 mL, 1.1268 mmol) were added to 6 (0.3249 g, 0.3756 mmol), and the mixture was refluxed at 90 °C for 2 h. After which, the mixture was concentrated, and THF (8 mL), DiEA (5 equiv), and the respective halide (3 equiv) were added. The reaction mixture was stirred at room temperature for 12 h and filtered. The resin was washed with MeOH (10 mL \times 3) and CH₂Cl₂ (10 mL \times 3), and the combined organic layer was concentrated and purified by column chromatography (EtOAc–hexane = 2:1 and then MeOH–CH₂Cl₂ = 1:10) to give 7.

1-Allyl-7-butylxanthine (7b). ¹H NMR (CDCl₃, 300 MHz): δ 10.40 (s, NH, 1H), 7.60 (s, CH, 1H), 6.00–5.87 (m, NCH₂CHCH₂, 1H), 5.30–5.18 (m, NCH₂CHCH₂, 2H), 4.62–4.60 (d, *J* = 5.6 Hz, NCH₂CHCH₂, 2H), 4.31–4.26 (t, *J* = 7.1 Hz, NCH₂CH₂CH₂CH₃, 2H), 1.91–1.81 (m, NCH₂CH₂CH₂CH₃, 2H), 1.42–1.30 (m, NCH₂CH₂CH₂CH₃, 2H), 0.99–0.94 (t, *J* = 7.5 Hz, NCH₂CH₂CH₂CH₃, 3H). ¹³C NMR (CDCl₃, 300 MHz): δ 155.1, 151.1, 147.3, 141.0, 132.1, 117.5, 107.0, 47.1, 42.8, 32.7, 19.6, 13.5. Mass spectrum (EI): *m/z* 248.2 (M⁺). Exact mass calcd for C₁₂H₁₆N₄O₂: *m/z* 248.1273. Found: 248.1272. Overall yield: 35%.

7-Butyl-1-phenylxanthine (7c). ¹H NMR (CDCl₃, 300 MHz): δ 7.70 (s, CH, 1H), 7.54–7.41 (m, ArH, 3H), 7.29–7.26 (m, ArH, 2H), 4.28–4.23 (t, *J* = 7.3 Hz, NCH₂CH₂CH₂CH₃, 2H), 1.90–1.80 (m, NCH₂CH₂CH₂CH₃, 2H), 1.41–1.31 (m, NCH₂CH₂CH₂CH₃, 2H), 0.96–0.91 (t, *J* = 7.3 Hz, NCH₂CH₂CH₂CH₃, 3H). ¹³C NMR (CDCl₃, 300 MHz): δ 155.5, 151.5, 147.9, 141.3, 134.9, 129.4, 129.2, 128.8, 107.2, 42.2, 32.7, 19.6, 13.4. Mass spectrum (EI): *m/z* 283.9 (M⁺). Exact mass calcd for C₁₅H₁₆N₄O₂: *m/z* 284.1273. Found: 284.1270. Overall yield: 34%.

1-Benzyl-7-butylxanthine (7d). ¹H NMR (CDCl₃, 300 MHz): δ 10.55 (s, NH, 1H), 7.60 (s, CH, 1H), 7.50–7.47 (m, ArH, 2H), 7.32–7.24 (m, ArH, 3H), 5.17 (s, ArCH₂, 2H), 4.30–4.25 (t, *J* = 7.1 Hz, NCH₂CH₂CH₂CH₃, 2H), 1.90–1.80 (m, NCH₂CH₂CH₂CH₃, 2H), 1.41–1.29 (m, NCH₂CH₂CH₂CH₃, 2H), 0.98–0.93 (t, *J* = 7.3 Hz, NCH₂CH₂CH₂CH₃, 3H). ¹³C NMR (CDCl₃, 300 MHz): δ 155.4, 151.4, 147.3, 141.0, 137.2, 128.8, 128.4, 127.5, 107.0, 47.0, 43.9, 32.7, 19.5, 13.5. Mass spectrum (EI): *m/z* 298.2 (M⁺). Exact mass calcd for C₁₆H₁₈N₄O₂: *m/z* 298.1430. Found: 298.1435. Overall yield: 29%.

7-Benzyl-1-hexylxanthine (7e). ¹H NMR (CDCl₃, 300 MHz): δ 11.26 (s, NH, 1H), 7.62 (s, CH, 1H), 7.44–7.35 (m, ArH, 5H), 5.48 (s, ArCH₂, 2H), 3.99–3.94 (t, *J* = 7.3 Hz, NCH₂CH₂CH₂CH₂CH₂CH₃, 2H), 1.64–1.62 (m, NCH₂CH₂CH₂CH₂CH₂CH₃, 2H), 1.31–1.25 (m, NCH₂CH₂CH₂CH₂CH₂CH₃, 6H), 0.89–0.85 (t, *J* = 6.1 Hz, CH₃, 3H). ¹³C NMR (CDCl₃, 300 MHz): δ 155.7, 151.4, 147.2, 140.8, 134.9, 129.1, 128.7, 128.2, 107.0, 50.3, 40.9, 31.5, 28.0, 26.6, 22.5, 14.0. Mass spectrum (EI): *m/z* 326.0 (M⁺). Exact mass calcd for C₁₈H₂₂N₄O₂: *m/z* 326.1743. Found: 326.1740. Overall yield: 25%.

7-Benzyl-1-phenylxanthine (7f). ^1H NMR (CDCl_3 , 300 MHz): δ 11.47 (s, NH, 1H), 7.69 (s, CH, 1H), 7.53–7.25 (m, ArH, 10H), 5.44 (s, CH_2 , 2H). ^{13}C NMR (CDCl_3 , 300 MHz): δ 155.7, 151.4, 147.8, 141.2, 134.8, 134.7, 129.3, 129.1, 128.8, 128.8, 128.4, 107.1, 50.5. Mass spectrum (EI): m/z 318.0 (M⁺). Exact mass calcd for $\text{C}_{18}\text{H}_{14}\text{N}_4\text{O}_2$: m/z 318.1117. Found: 318.1118. Overall yield: 30%.

1,7-Dibenzylxanthine (7g). ^1H NMR ($\text{DMSO}-d_6$, 300 MHz): δ 8.21 (s, CH, 1H), 7.33–7.26 (m, ArH, 10H), 5.46 (s, NCH_2 , 2H), 4.99 (s, NCH_2 , 2H). ^{13}C NMR ($\text{DMSO}-d_6$, 300 MHz): δ 155.0, 150.9, 148.0, 143.1, 137.7, 137.0, 128.7, 128.2, 128.0, 127.5, 127.3, 127.0, 105.7, 48.9, 42.8. Mass spectrum (EI): m/z 331.9 (M⁺). Exact mass calcd for $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_2$: m/z 332.1273. Found: 332.1274. Overall yield: 23%.

1-Allyl-7-benzylxanthine (7h). ^1H NMR (CDCl_3 , 300 MHz): δ 11.60 (s, NH, 1H), 7.63 (s, CH, 1H), 7.40–7.33 (m, ArH, 5H), 5.99–5.79 (m, $\text{NCH}_2\text{CHCH}_2$, 1H), 5.48 (s, NCH_2 , 2H), 5.28–5.09 (m, $\text{NCH}_2\text{CHCH}_2$, 2H), 4.61–4.59 (d, $J = 5.6$ Hz, $\text{NCH}_2\text{CHCH}_2$, 2H). ^{13}C NMR (CDCl_3 , 300 MHz): δ 155.3, 151.2, 147.5, 141.0, 135.3, 132.1, 129.1, 128.8, 128.2, 117.4, 106.9, 50.4, 42.7. Mass spectrum (EI): m/z 282.0 (M⁺). Exact mass calcd for $\text{C}_{15}\text{H}_{14}\text{N}_4\text{O}_2$: m/z 282.1117. Found: 282.1115. Overall yield: 27%.

7-Benzyl-3-methyl-1-phenylxanthine (7i). ^1H NMR (CDCl_3 , 300 MHz): δ 7.55 (s, CH, 1H), 7.46–7.16 (m, ArH, 10H), 5.40 (s, CH_2 , 2H), 3.54 (s, CH_3 , 3H). ^{13}C NMR (CDCl_3 , 300 MHz): δ 155.2, 151.6, 149.5, 141.1, 135.4, 129.4, 129.1, 128.7, 128.2, 107.2, 50.4, 29.8. Mass spectrum (EI): m/z 332.0 (M⁺). Exact mass calcd for $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_2$: m/z 332.1273. Found: 332.1274. Overall yield: 20%.

7-Benzyl-1-phenyl-3-propargylxanthine (7j). ^1H NMR (CDCl_3 , 300 MHz): δ 7.65 (s, CH, 1H), 7.53–7.25 (m, ArH, 10H), 5.47 (s, NCH_2 , 2H), 4.91–4.90 (d, $J = 2.5$ Hz, NCH_2CCH , 2H), 2.28–2.27 (t, $J = 2.4$ Hz, CH_2CCH , 1H). ^{13}C NMR (CDCl_3 , 300 MHz): δ 155.0, 150.7, 148.2, 141.3, 135.1, 134.9, 129.4, 129.1, 128.8, 128.7, 128.4, 107.4, 72.0, 50.5, 32.6. Mass spectrum (EI): m/z 356.0 (M⁺). Exact mass calcd for $\text{C}_{21}\text{H}_{16}\text{N}_4\text{O}_2$: m/z 356.1273. Found: 356.1272. Overall yield: 19%.

1-Allyl-7-benzyl-3-methylxanthine (7k). ^1H NMR (CDCl_3 , 500 MHz): δ 7.54 (s, CH, 1H), 7.38–7.32 (m, ArH, 5H), 5.96–5.88 (m, $\text{NCH}_2\text{CHCH}_2$, 1H), 5.49 (s, NCH_2 , 2H), 5.28–5.17 (m, $\text{NCH}_2\text{CHCH}_2$, 2H), 4.63–4.62 (m, NCH_2 , 2H), 3.57 (s, NCH_3 , 3H). ^{13}C NMR (CDCl_3 , 500 MHz): δ 154.8, 151.2, 149.0, 140.9, 135.2, 132.3, 129.1, 128.7, 128.0, 117.5, 107.0, 50.3, 43.4, 29.7. Mass spectrum (EI): m/z 296.0 (M⁺). Exact mass calcd for $\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_2$: m/z 296.1273. Found: 296.1280. Overall yield: 20%.

1-Allyl-7-benzyl-3-propargylxanthine (7l). ^1H NMR (CDCl_3 , 500 MHz): δ 7.58 (s, CH, 1H), 7.39–7.33 (m, ArH, 5H), 5.96–5.88 (m, $\text{NCH}_2\text{CHCH}_2$, 1H), 5.49 (s, NCH_2 , 2H), 5.29–5.18 (m, $\text{NCH}_2\text{CHCH}_2$, 2H), 4.88–4.87 (d, $J = 1.9$ Hz, NCH_2CCH , 2H), 4.64–4.62 (m, $\text{NCH}_2\text{CHCH}_2$, 2H), 2.25–2.25 (t, $J = 2.2$ Hz, NCH_2CCH , 1H). ^{13}C NMR (CDCl_3 , 500 MHz): δ 154.7, 150.4, 147.7, 141.1, 135.0, 132.0, 129.1, 128.7, 128.2, 117.8, 107.2, 77.6, 71.8, 50.4, 43.5, 32.5. Mass spectrum (EI): m/z 320.0 (M⁺). Exact mass

calcd for $\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}_2$: m/z 320.1273. Found: 320.1275. Overall yield: 19%.

7-Benzyl-1,3-diallylxanthine (7m). ^1H NMR (CDCl_3 , 500 MHz): δ 7.54 (s, CH, 1H), 7.38–7.33 (m, ArH, 5H), 6.00–5.88 (m, $\text{NCH}_2\text{CHCH}_2$, 2H), 5.49 (s, NCH_2 , 2H), 5.32–5.19 (m, $\text{NCH}_2\text{CHCH}_2$, 4H), 4.71–4.62 (m, $\text{NCH}_2\text{CHCH}_2$, 4H). ^{13}C NMR (CDCl_3 , 500 MHz): δ 154.8, 150.7, 148.5, 141.0, 135.1, 132.2, 131.5, 129.1, 128.7, 128.1, 118.0, 117.5, 107.0, 50.3, 45.3, 43.3. Mass spectrum (EI): m/z 321.8 (M⁺). Exact mass calcd for $\text{C}_{18}\text{H}_{18}\text{N}_4\text{O}_2$: m/z 322.1430. Found: 322.1435. Overall yield: 23%.

1-Allyl-3,7-dibenzylxanthine (7n). ^1H NMR (CDCl_3 , 300 MHz): δ 7.46 (s, CH, 1H), 7.42–7.41 (m, ArH, 2H), 7.29–7.14 (m, ArH, 8H), 5.91–5.78 (m, $\text{NCH}_2\text{CHCH}_2$, 1H), 5.40 (s, NCH_2 , 2H), 5.19–5.08 (m, NCH_2 and $\text{NCH}_2\text{CHCH}_2$, 4H), 4.56–4.54 (m, $\text{NCH}_2\text{CHCH}_2$, 2H). ^{13}C NMR (CDCl_3 , 300 MHz): δ 154.8, 151.0, 148.7, 140.9, 136.4, 135.1, 132.2, 129.1, 128.7, 128.5, 128.2, 127.8, 117.5, 107.1, 50.3, 46.6, 43.4. Mass spectrum (EI): m/z 371.7 (M⁺). Exact mass calcd for $\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_2$: m/z 372.1586. Found: 372.1584. Overall yield: 24%.

3-Allyl-7-benzyl-1-phenylxanthine (7o). ^1H NMR (CDCl_3 , 300 MHz): δ 7.54 (s, CH, 1H), 7.45–7.17 (m, ArH, 10H), 6.00–5.87 (m, $\text{NCH}_2\text{CHCH}_2$, 1H), 5.40 (s, NCH_2 , 2H), 5.30–5.15 (m, $\text{NCH}_2\text{CHCH}_2$, 2H), 4.67–4.65 (d, $J = 5.9$ Hz, $\text{NCH}_2\text{CHCH}_2$, 2H). ^{13}C NMR (CDCl_3 , 300 MHz): δ 155.2, 151.1, 149.0, 141.2, 135.3, 135.0, 131.4, 129.3, 129.1, 128.7, 128.7, 128.4, 118.6, 107.3, 50.4, 45.6. Mass spectrum (EI): m/z 358.1 (M⁺). Exact mass calcd for $\text{C}_{21}\text{H}_{18}\text{N}_4\text{O}_2$: m/z 358.1430. Found: 358.1422. Overall yield: 23%.

3,7-Dibenzyl-1-phenylxanthine (7p). ^1H NMR (CDCl_3 , 300 MHz): δ 7.54–7.15 (m, CH and ArH, 16H), 5.36 (s, NCH_2 , 2H), 5.20 (s, NCH_2 , 2H). ^{13}C NMR (CDCl_3 , 300 MHz): δ 155.1, 151.4, 149.1, 141.0, 136.2, 135.3, 135.0, 129.3, 129.2, 129.1, 128.7, 128.6, 128.5, 128.4, 127.9, 107.3, 50.3, 46.7. Mass spectrum (EI): m/z 408.1 (M⁺). Exact mass calcd for $\text{C}_{25}\text{H}_{20}\text{N}_4\text{O}_2$: m/z 408.1586. Found: 408.1588. Overall yield: 20%.

1-Allyl-7,8-dimethylxanthine (7q). ^1H NMR ($\text{DMSO}-d_6$, 300 MHz): δ 11.76 (s, NH, 1H), 5.90–5.75 (m, $\text{NCH}_2\text{CHCH}_2$, 1H), 5.08–5.00 (m, $\text{NCH}_2\text{CHCH}_2$, 2H), 4.42–4.40 (d, $J = 4.9$ Hz, $\text{NCH}_2\text{CHCH}_2$, 2H), 3.78 (s, NCH_3 , 3H), 2.36 (s, CCH_3 , 3H). ^{13}C NMR ($\text{DMSO}-d_6$, 300 MHz): δ 154.0, 151.0, 150.0, 146.3, 132.8, 115.4, 105.8, 41.0, 30.8, 12.2. Mass spectrum (EI): m/z 219.9 (M⁺). Exact mass calcd for $\text{C}_{10}\text{H}_{12}\text{N}_4\text{O}_2$: m/z 220.0960. Found: 220.0960. Overall yield: 16%.

7,8-Dimethyl-1-phenylxanthine (7r). ^1H NMR ($\text{DMSO}-d_6$, 300 MHz): δ 11.85 (s, NH, 1H), 7.48–7.21 (m, ArH, 5H), 3.76 (s, NCH_3 , 3H), 2.39 (s, CCH_3 , 3H). ^{13}C NMR ($\text{DMSO}-d_6$, 300 MHz): δ 155.0, 151.6, 150.9, 147.2, 136.0, 129.4, 128.7, 127.8, 106.6, 31.3, 12.7. Mass spectrum (EI): m/z 255.9 (M⁺). Exact mass calcd for $\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}_2$: m/z 256.0960. Found: 256.0960. Overall yield: 15%.

1-Allyl-3-benzyl-7,8-dimethylxanthine (7s). ^1H NMR (CDCl_3 , 300 MHz): δ 7.41–7.17 (m, ArH, 5H), 5.90–5.72 (m, $\text{NCH}_2\text{CHCH}_2$, 1H), 5.23–5.03 (m, ArCH₂ and $\text{NCH}_2\text{CHCH}_2$, 4H), 4.54–4.53 (d, $J = 5.6$ Hz, $\text{NCH}_2\text{CHCH}_2$, 2H), 3.81 (s, NCH_3 , 3H), 2.38 (s, CCH_3 , 3H). ^{13}C NMR

(CDCl₃, 300 MHz): δ 154.8, 151.0, 150.8, 147.8, 136.6, 132.5, 128.6, 128.4, 127.7, 117.2, 107.5, 46.4, 43.2, 31.8, 13.1. Mass spectrum (EI): m/z 310.2 (M⁺). Exact mass calcd for C₁₇H₁₈N₄O₂: m/z 310.1430. Found: 310.1430. Overall yield: 14%.

1-Phenyl-3,7,8-trimethylxanthine (7t). ¹H NMR (CDCl₃, 300 MHz): δ 7.46–7.16 (m, ArH, 5H), 3.82 (s, NCH₃, 3H), 3.52 (s, NCH₃, 2H), 2.42 (s, CCH₃, 3H). ¹³C NMR (CDCl₃): δ 155.2, 151.7, 151.1, 148.6, 135.7, 129.3, 128.8, 128.6, 107.7, 31.9, 29.7, 13.1. Mass spectrum (EI): m/z 270.1 (M⁺). Exact mass calcd for C₁₄H₁₄N₄O₂: m/z 270.1117. Found: 270.1110. Overall yield: 14%.

1-Allyl-7-methyl-8-phenylxanthine (7u). ¹H NMR (CDCl₃, 500 MHz): δ 10.26 (s, NH, 1H), 7.71–7.53 (m, ArH, 5H), 5.99–5.91 (m, NCH₂CHCH₂, 1H), 5.30–5.19 (m, NCH₂CHCH₂, 2H), 4.65–4.63 (m, NCH₂CHCH₂, 2H), 4.06 (s, CH₃, 3H). ¹³C NMR (CDCl₃, 500 MHz): δ 155.6, 152.5, 151.1, 146.7, 132.2, 130.5, 129.3, 128.9, 128.0, 117.4, 108.5, 42.7, 33.9. Mass spectrum (ESI): m/z 283.1 (M + H⁺). Exact mass calcd for C₁₅H₁₄N₄O₂: m/z 282.1117. Found: 283.1190 (M + H⁺). Overall yield: 7%.

1-Allyl-3,7-dimethyl-8-phenylxanthine (7v). ¹H NMR (CDCl₃, 500 MHz): δ 7.69–7.52 (m, ArH, 5H), 5.99–5.91 (m, NCH₂CHCH₂, 1H), 5.31–5.19 (m, NCH₂CHCH₂, 2H), 4.67–4.66 (m, NCH₂CHCH₂, 2H), 4.06 (s, NCH₃, 3H), 3.63 (s, NCH₃, 3H). ¹³C NMR (CDCl₃, 500 MHz): δ 155.2, 152.2, 151.3, 148.5, 132.4, 130.4, 129.2, 128.9, 128.4, 117.4, 108.6, 43.3, 33.9, 29.7. Mass spectrum (ESI): m/z 297.1 (M + H⁺). Exact mass calcd for C₁₆H₁₆N₄O₂: m/z 296.1273. Found: 297.1346 (M + H⁺). Overall yield: 6%.

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Supporting Information Available. ¹H and ¹³C NMR spectra of all compounds, X-ray structure of **7p**, and IR spectra of resins **1–6**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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