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A simple synthesis of di(uracilyl)aryl methanes and 1,ω-bis[di(uracilyl)methyl]benzenes

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Abstract—Di(uracilyl)aryl methanes and their homologues, 1,ω-bis[di(uracilyl)methyl]benzenes, have been synthesized in good yields through the HBr–acetic acid catalyzed condensation of 1-alkyl-/1,3-dialkyluracil derivatives with readily available aryl aldehydes and dialdehydes.
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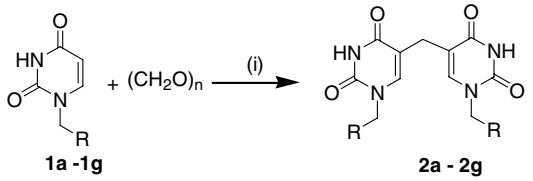
The chemistry of diaryl and triarylmethane (TAM) derivatives has witnessed a rapid growth[1] because of the interesting properties associated with their derivatives. The classical chemistry of dyes relies mainly on the triarylmethyl core because of its brilliant colours and high tinctorial strength, whereas the acid-labile nature of the trityl group has made it a very useful protecting group for nucleosides, carbohydrates, etc.[2] A number of TAM derivatives have found medicinal applications. Phenol derivatives of TAM exhibit antitumour activity and inhibitory activity towards histidine protein kinase.[3] Malachite Green has long been used to control fungal and protozoan infections in fish and it shows selective phototoxicity towards tumour cells.[4] The cation complexing ability of Malachite Green-based crown ether has found application in the ionic-conductivity switching of composite films.[5]

Tri-heteroaryl or mixed heteroaryl methanes, due to the presence of heteroatoms like *O*, *S*, *N* or their combinations in the aryl ring provide additional binding sites and chemical pliability,[6] which has been advantageously used for obtaining supramolecular architectures.[7]

Amongst heterocycles, pyrimidine-2,4(1*H*,3*H*)-diones are the most versatile for creating supramolecular architectures both in living systems[8] and synthetic models.[9] The H-bonding interactions in the Watson–Crick model[8] provide the basis of double/multiple strand DNA and the metal ion interactions of phosphate groups stabilize these strands. The metal ion–π interactions of the heterocyclic rings and charge–electron interactions with the heteroatoms of nucleic bases lead to the stabilization of single strands and stimulate their catalytic processes.[10,11] Advances in X-ray structure resolutions have provided further an insight into the nucleic base–metal ion interactions.

However, the synthesis of triarylmethanes based on uracil derivatives has not attracted attention.[12] The availability of such scaffolds is expected to provide many new entities for supramolecular interactions. Herein, we report a general synthetic approach for the synthesis of di(uracilyl) methanes, di(uracilyl)aryl methanes and 1,ω-bis[di(uracilyl)methyl]benzenes. It is noteworthy that the condensations of electron-rich enamines, namely indoles and pyrroles with aldehydes to give heteroarylmethanes are well documented. In contrast, this manuscript provides a first general protocol where the electron-deficient enamine moiety of uracil can be readily used to achieve similar di(uracilyl)aryl methanes and their homologues.

1-Benzyluracil (**1**) on heating with paraformaldehyde (0.5 equiv) in HBr–acetic acid (33%) in an oil bath at



Scheme 1. Reagent and condition: (i) HBr–acetic acid (33%), 120 °C.

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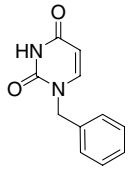
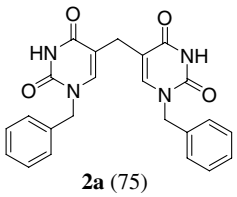
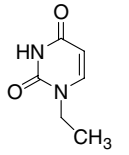
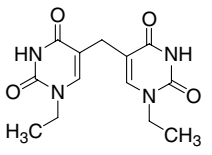
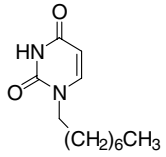
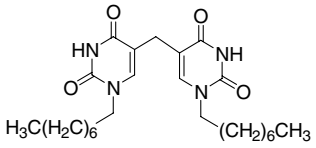
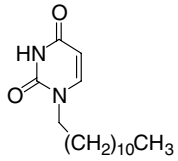
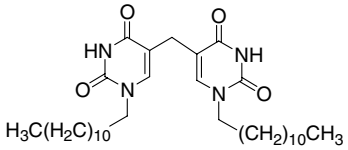
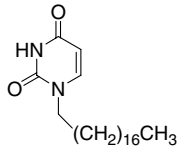
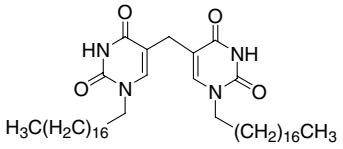
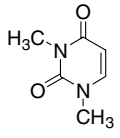
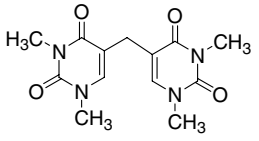
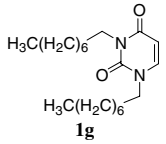
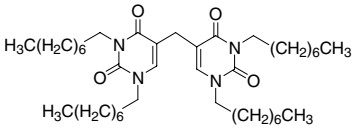
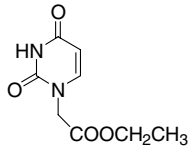
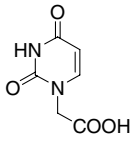
Table 1. Synthesis of di(uracilyl)methanes

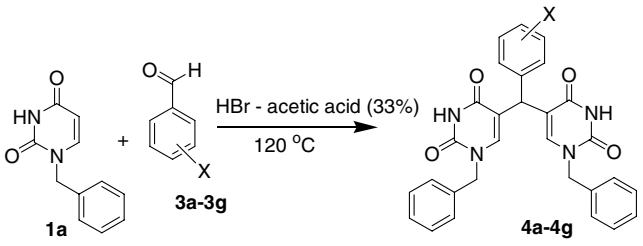
Entry	Substrate **1**	Product **2** (yield %)
1	 **1a**	 **2a** (75)
2	 **1b**	 **2b** (68)
3	 **1c**	 **2c** (70)
4	 **1d**	 **2d** (72)
5	 **1e**	 **2e** (70)
6	 **1f**	 **2f** (70)
7	 **1g**	 **2g** (65)
8	 **1h**	 **1i** (95)

120 °C provided **2a** (75%), mp 260 °C, FAB mass *m*/*z* 416 (M^+) (Scheme 1).[13] In its ^{1}H NMR spectrum, the presence of two 2H singlets at δ 3.29 and δ 7.88, respectively, due to the methylene group and C-6H of uracil shows the connectivity of the methylene carbon with two uracil moieties at C-5 and along with other data (^{13}C NMR, elemental analysis) corroborates structure **2a**.

Similarly, 1-substituted uracils **1b–g** under the identified reaction conditions gave di(uracilyl)methanes **2b–g** (Table 1). The presence of an electron-withdrawing CH_2COOEt group at *N*-1 in **1h** restricted its reactivity towards paraformaldhyde and only hydrolyzed uracil derivative **1i** was isolated.

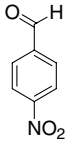
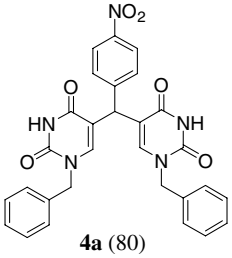
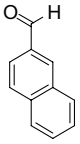
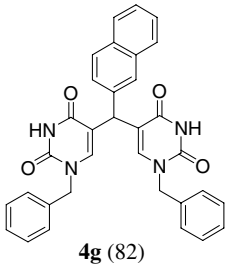
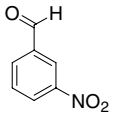
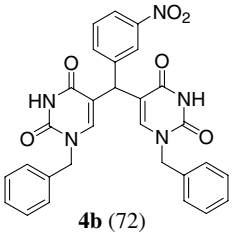
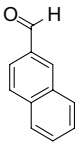
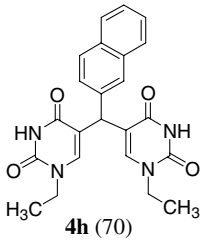
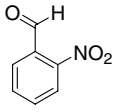
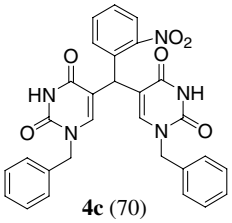
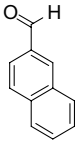
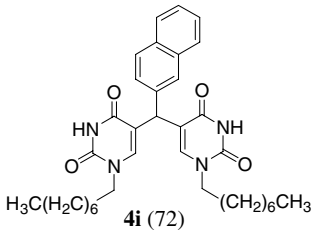
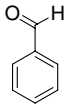
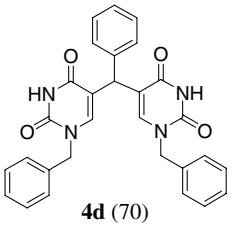
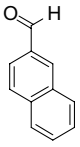
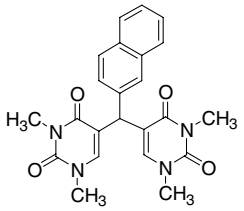
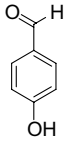
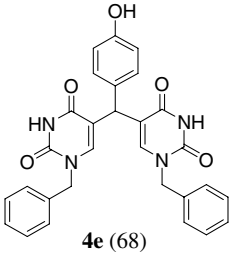
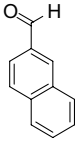
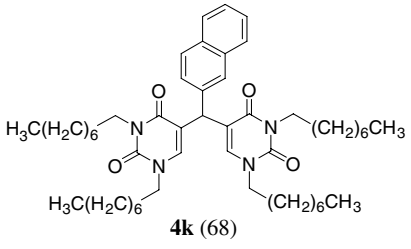
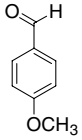
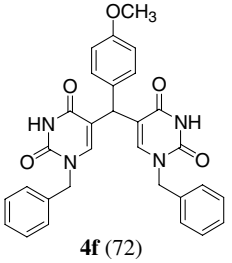
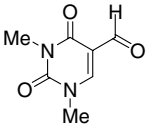
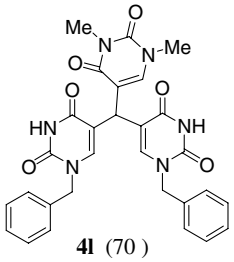
In order to extend these reactions towards the synthesis of diheteroaryl aryl methane derivatives, the reactions of **1** with various aryl aldehydes were investigated. Stirring a solution of **1a** in HBr–acetic acid (33%) with *p*-nitrobenzaldehdyde at 120 °C gave **4a** as a yellow solid, mp 236 °C, FAB mass *m*/*z* 537 (M^+) (Scheme 2 and Table 2, entry 1). Similarly, *ortho*- and *meta*-nitrobenzaldehydes and benzaldehdyde underwent condensation with **1a** at 120 °C to provide **4b–d** in 70–72% yields (Table 2). However, **1a** on reaction with *p*-methoxybenzaldehyde at 120 °C gave **4e** (65%). The formation of **4e** could be presumed to proceed through either formation of **4f** and subsequent demethylation or demethylation of **3f** and condensation with **1a** or through both. Compound **4e** could also be obtained by condensation of **1a** with *p*-hydroxybenzaldehyde **3e** (68%). On reaction of **1a** with **3f** at 60 °C, **4f** (72%) was isolated. 1,3-Dimethyl-5-formyluracil (**3h**) underwent facile condensation with **1a** to give unsymmetrical tris(uracilyl)methane **4l**, 70%. However, the aliphatic aldehydes CH_3CHO $(CH_3)_2CHO$ and $(CH_3)_3CHO$, presumably due to their instability under the reaction conditions, failed to provide the respective derivatives of **4** and unreacted **1a** was recovered. Compounds **2** and **4** could be obtained on 5 g scale and did not require chromatography for purification. Pure samples were obtained through crystallization.

Keeping in mind that the presence of a fluorescent group on the methylene bridge of di(uracilyl)methane derivatives **4**, could provide a simple means for investigating their interactions, we planned to synthesize fluorescent derivatives of **4**. The reaction of **1a** with naphthalene-2-aldehyde in HBr–acetic acid gave **4g** (82%); mp 210 °C.

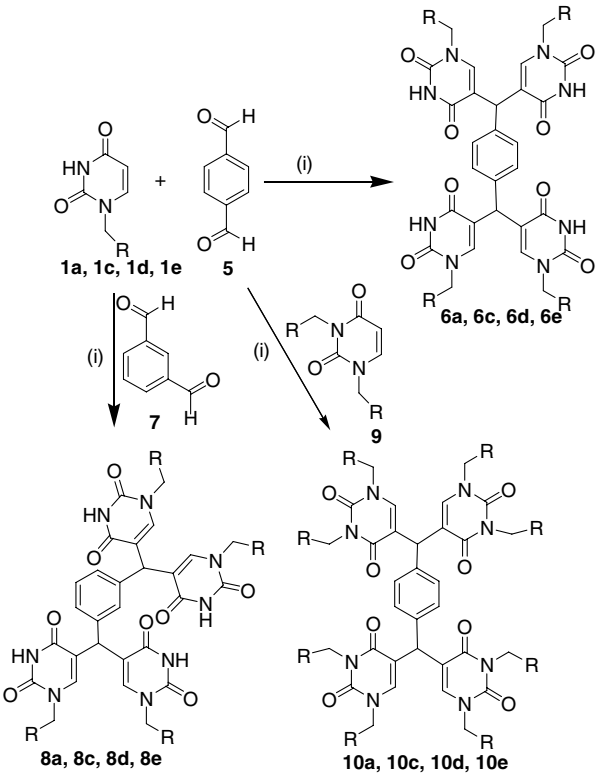


Scheme 2.

Table 2. Synthesis of di (uracilyl)aryl methanes (**4**)

Entry	Aldehyde	Uracil	Product **4** (yield, %)	Entry	Aldehyde	Uracil	Product **4** (yield, %)
1	 **3a**	**1a**	 **4a** (80)	7	 **3g**	**1a**	 **4g** (82)
2	 **3b**	**1a**	 **4b** (72)	8	 **3g**	**1b**	 **4h** (70)
3	 **3c**	**1a**	 **4c** (70)	9	 **3g**	**1c**	 **4i** (72)
4	 **3d**	**1a**	 **4d** (70)	10	 **3g**	**1f**	 **4j** (70)
5	 **3e**	**1a**	 **4e** (68)	11	 **3g**	**1g**	 **4k** (68)
6	 **3f**	**1a**	 **4f** (72)	12	 **3h**	**1a**	 **4l** (70)

The reactions of 1- and 1,3-disubstituted uracils with naphthalene-2-aldehyde gave the respective di(uracilyl)-2-naphthylmethanes **4h–k** in 68–72% yields (Table 2, entries 7–11). The reaction of anthracene-9-aldehyde



Scheme 3. In **6**, **8**, **10**: **a**, R = C_6H_5; **c**, R = $CH_2(CH_2)_5CH_3$; **d**, R = $CH_2(CH_2)_9CH_3$; **e**, R = $CH_2(CH_2)_{15}CH_3$. Reagent and condition: (i) HBr–acetic acid (33%); 120 °C.

with **1a** in HBr–acetic acid resulted in deformylation of the aldehyde and the respective di(uracilyl) anthracenyl methane was not isolated.

The reactions of 1-alkyluracils with terephthaldehdye gave 1,4-bis[di(uracilyl)methyl]benzenes **6a** and **6c**–**e**. Similarly, reaction of isophthaldehyde with 1-alkyluracils gave 1,3-bis[di(uracilyl)methyl]benzenes **8a** and **8c**–**e**. The presence of an alkyl substituent at N-3 of uracil did not affect its reactivity towards aryl dialdehydes. The condensation of 1,3-dialkyluracils (**9**) with terephthaldehyde gave compounds **10a** and**10c**–**e** (Scheme 3).

Thus, the condensation of readily available[14] 1-alkyl-, and 1,3-dialkyluracil derivatives with aromatic aldehydes and dialdehydes provides a versatile approach for the synthesis of di(uracilyl)aryl methanes and their homologues Significantly, their synthesis in multigram quantities, ease of purification through crystallization and their high yields are advantages.

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References and notes

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13. *General procedure:* 1-alkyl- or 1,3-dialkyl uracil derivatives **1** were heated in an oil bath at 120 °C with the aryl aldehyde (0.5 equiv) (**3**) or 1,ω-dialdehyde (0.25 equiv) (**5** or **7**) in HBr–acetic acid (33%). On completion, the reaction mixture was cooled to room temp. and was poured onto ice. The solid that separated was filtered and was crystallized from CH_3CN or CH_3CN–ethanol to afford pure compounds.
Di(uracilyl)methane **2c**, white solid; 70%; mp 83 °C (CH_3CN); FAB mass M^+ *m*/*z* 460 (M^+); ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.9 Hz, 6H, 2 × CH_3), 1.28 (br s, 24H, 12 × CH_2), 3.27 (s, 2H, C5-CH_2), 3.69 (t, *J* = 6.9 Hz, 4H, 2 × N1–CH_2), 7.43 (s, 2H, C6-H), 8.78 (s, 2H, 2 × NH); ^{13}C NMR (normal/DEPT-135) (75 MHz, $CDCl_3$): δ 14.1 (+ve, CH_3), 22.6 (−ve, CH_2), 23.6 (−ve, CH_2), 26.4 (−ve, CH_2), 29.1 (−ve, CH_2), 31.7 (−ve, CH_2), 48.8 (−ve, CH_2), 110.4 (absent, ArC), 143.3 (+ve, C6-H), 150.7 (absent, CO), 164.2 (absent, CO). Found C 65.28; H 8.70; N 12.10. $C_{25}H_{40}N_4O_4$ requires C 65.19, H 8.75; N

12.16%. *Di(uracilyl) 2-naphthyl methane* **4i**, white solid; 72%; mp 130 °C (CH_3CN); FAB mass M^+ *m/z* 586 (M^+); ^1H NMR (300 MHz, $CDCl_3$): δ 0.85 (t, $J = 6.5$ Hz, 6H, $2 \times CH_3$), 1.23 (br s, 24H, $12 \times CH_2$), 3.64 (t, $J = 6.2$ Hz, 4H, $2 \times$ N1–CH_2), 3.51 (s, 1H, C5-CH), 7.13 (s, 2H, C6-H), 7.44–7.49 (m, 3H, ArH), 7.61 (s, 2H, ArH), 7.79 (d, $J = 8.0$ Hz, 2H, ArH), 8.80 (s, 2H, $2 \times$ NH); ^{13}C NMR (normal/DEPT-135) (75 MHz, $CDCl_3$): δ 13.9 (+ve, CH_3), 22.5 (−ve, CH_2), 26.2 (−ve, CH_2), 28.9 (−ve, CH_2), 29.0 (−ve, CH_2), 31.6 (−ve, CH_2), 41.0 (+ve, CH), 48.9 (−ve, CH_2), 113.2 (absent, ArC), 126.0 (+ve ArCH), 126.3 (+ve, ArCH), 126.5 (+ve, ArCH), 127.5 (+ve, ArCH), 127.9 (+ve, ArCH), 128.4 (+ve, ArCH), 129.1 (+ve, ArCH), 132.4 (absent, ArC), 133.3 (absent, ArC), 136.6 (absent, ArC), 144.7 (+ve, C6-H), 150.6 (absent, CO), 163.3 (absent, CO). Found C 71.68; H 7.85; N 9.57. $C_{35}H_{46}N_4O_4$ requires C 71.64, H 7.90; N 9.55.

1,4-bis[di(uracilyl)methyl benzene **6c**, white solid; 60%; mp 245 °C(CH_3CN); FAB mass M^+ *m/z* 994 (M^+); ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, $J = 6.9$ Hz, 12H, $4 \times CH_3$), 1.26 (br s, 48H, $24 \times CH_2$), 3.68 (t, $J = 6.9$ Hz, 8H, $4 \times$ N1–CH_2), 5.12 (s, 2H, $2 \times$ C5-CH), 7.15 (s, 4H, C6-H), 7.22 (s, 4H, ArH), 8.71 (s, 4H, $4 \times$ NH); ^{13}C NMR (normal/DEPT-135) (75 MHz, $CDCl_3$): δ 14.1 (+ve, CH_3), 22.5 (−ve, CH_2), 26.4 (−ve, CH_2), 29.1 (−ve, CH_2), 31.6 (−ve, CH_2), 32.0 (−ve, CH_2), 42.5 (+ve, CH), 49.0 (−ve, CH_2), 112.9 (absent, ArC), 121.0 (absent, ArC), 128.2 (+ve, ArCH), 137.9 (absent, ArC), 144.8 (+ve, C6-H), 150.7 (absent, CO), 163.5 (absent, CO). Found C 67.48; H 8.40; N 11.22. $C_{56}H_{82}N_8O_8$ requires C 67.58, H 8.30; N 11.26.

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