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Recent advances in the chemistry of triaryl- and triheteroarylmethanes

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Contents

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1. Introduction

Triarylmethanes (TAMs) have attracted the attention of many scientists mainly because of the interesting properties associated with their derivatives. The versatility of TAM is clear from their high end applications. For instance, simple triarylmethanes have been reported to be active against intestinal helminths, filariae, trichomonads, and trypanosomes[1] and the phenol derivatives of TAM have been known to exhibit antioxidant properties, antitumor activity, and inhibitory activity toward histidine protein kinase.[2]

Keywords: Triarylmethanes; Triheteroarylmethanes.

Abbreviations: Ar, aryl; Bt, benzotriazolyl; CAN, cerium(IV) ammonium nitrate; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DME, 1,2-dimethoxyethane; DMSO, dimethylsulfoxide; ISC, inter system crossing; INDO, intermediate neglect of differential overlap; LAH, lithium aluminum hydride; LDA, lithium diisopropylamide; NBS, *N*-bromosuccinimide; NLO, non-linear optical; OTf, triflate; PTSA, *p*-toluenesulfonic acid; PPA, polyphosphoric acid; TFA, trifluoroacetic acid; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TMS, trimethylsilyl; binap, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

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The acid-labile nature of the trityl group made it a celebrated protecting group for nucleosides, carbohydrates, etc.[3] The well-known dyes generated from TAM including Crystal Violet, Malachite Green, Sunset Orange, Pararosanilin, Victoria Blue, etc. (Fig. 1) exhibit stable quinoid structures.[4] Malachite Green has long been used to control the fungal and protozoan infections in fish[5] and it shows selective phototoxicity toward tumor cells.[6]

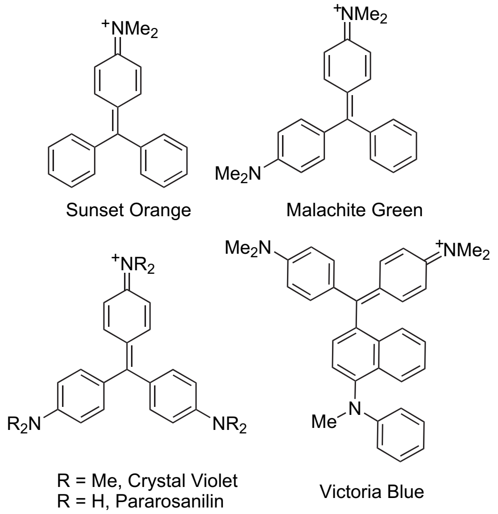


Figure 1.

TAM leucocyanides and dyes are useful in many photochemical reactions.[7] TAM derived from pyrene and terephthalaldehyde are used in polymer chemistry and they possess ferromagnetic properties. In addition, these molecules are potential synthons for the construction of complex three-dimensional network systems. Three known heterocyclic analogs of TAM are tri-2-thienylmethane, tri-2-furylmethane, and triindolylmethane (Fig. 2) and their chemistry has been investigated to some extent.

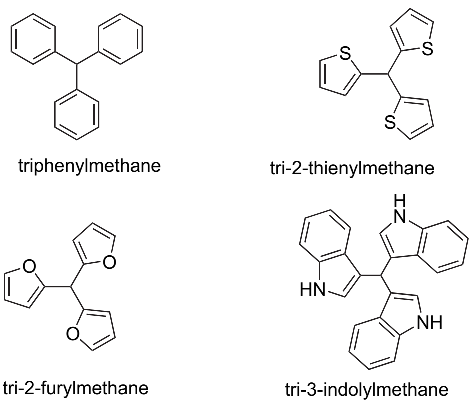


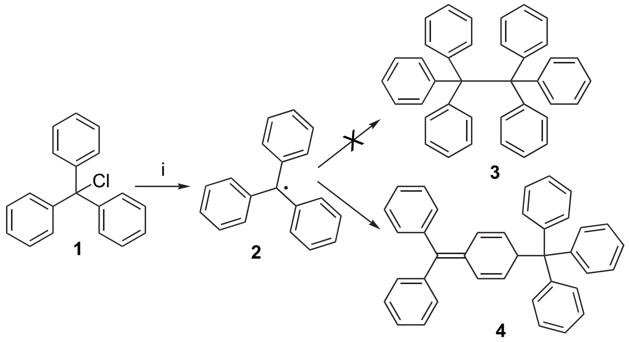
Figure 2.

The present report is aimed at highlighting the recent chemistry of triarylmethanes and at serving as a pointer to their diverse applications. The main aspects covered in the first part are the literature on triphenylmethyl radicals and cations, especially their synthesis and reactions. An account of TAM dyes and TAM leuco-derivatives is also provided in this part. Since the photochemical and photophysical aspects of TAM dyes were reviewed earlier,[8] such details have been excluded from this review. In the second part, the chemistry of symmetric triheteroarylmethanes like tri-2-thienylmethane, tri-2-furylmethane, and triindolylmethane is discussed.

2. Chemistry of triarylmethanes

2.1. TAM radicals

The experimental demonstration of the existence of the triphenylmethyl radical **2** by Gomberg is a milestone in the development of mechanistic organic chemistry.[9] The radical, prepared by the action of zinc powder on triphenylmethyl chloride **1** (Scheme 1), was shown to be stable for weeks in the dry crystalline state. The dimer of the triphenylmethyl radical was thought to be hexaphenylethane **3**, which was later disproved by the establishment of its correct quinoid structure **4** by Lankamp et al.[10–12] The trityl radical reacts readily with oxygen, yielding the corresponding peroxide and, with iodine, it forms the iodotriarylmethane. The peroxide on exposure to sulfuric acid is transformed into the triarylmethanol.[9]



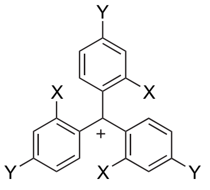
Scheme 1. (i) Zn/Ag.

Later, Gomberg prepared a radical more stable than **2** by substituting –OR groups on the phenyl rings.[13]

2.2. TAM carbenium ions

Trityl halides were the first source of stable carbocations and, later, tritylcarbinols were found to be more useful for the generation of carbocations.[14] Breslow et al. have investigated carbenium ions of the type **5**, with more than one group available for interaction with the cationic center (Fig. 3).[15] Substituents X contain heteroatoms that can coordinate to the cationic center in a process called intramolecular solvation, while substituents Y can offer resonance stabilization to the carbocation. Carbenium ions required for the studies were prepared from the corresponding carbinols, which in turn, were obtained by the reaction of lithiobenzene derivatives with benzophenone, ethyl benzoate or diethyl carbonate.

NMR and ultraviolet spectroscopy, $\mathrm{p}K_{\mathrm{R}}+$ measurements, and quenching studies of a series of such TAM cations with potentially coordinating side chains in the *ortho*



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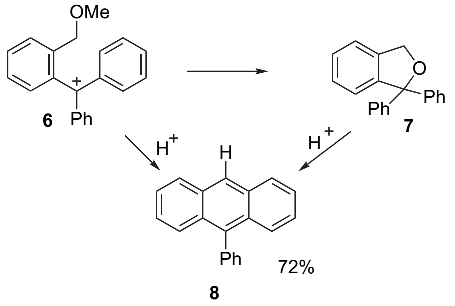
X = CH_2-S-Me, CH_2-O-Me etc.
Y = OMe, $N(Me)_2$, SMe etc.

Figure 3.

position have shown two types of ions, viz., those in which side chains are completely uncoordinated with the cation and those in which cyclization occurred with the side chain. The decomposition reaction of a solution of (*o*-methoxymethyl)triphenylmethyl cation **6** results in the formation of α,α-diphenyldihydroisobenzofuran **7**. This, on further treatment with acid, gets converted into 9-phenylanthracene **8**, thus exemplifying side-chain cyclization (Scheme 2).



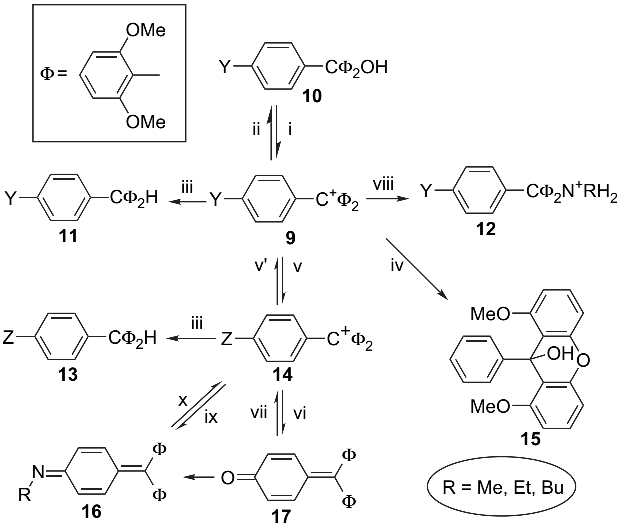
Scheme 2.

Triarylmethanols bearing *o*-methoxy groups on the phenyl ring were synthesized by Wada, and the reduction of the corresponding cation was investigated in various alcohols.[16] The high basicity of triarylmethane with additional methoxy groups at the *ortho* and *para* positions is explained by through-space interactions of a pair of 2p electrons of an *o*-methoxy oxygen with the empty 2p orbital of the resulting carbocation.

Wada et al. have also investigated the aromatic nucleophilic substitution of triarylcarbenium ions of the type **9** [$(4\text{-}YC_6H_4)C\Phi_2]^+$ where Φ=2,6-$(OMe)_2C_6H_3$; Y=OMe, NMe_2, Cl, OH.[17] Depending on the reaction conditions, the carbenium salts gave different products (**10–17**, Scheme 3). Arnett et al. have investigated the thermodynamic stability of such carbocations in sulfolane.[18]

2.3. TAM dyes

The photochemical and photophysical properties of triphenylmethane dyes in solid and liquid media were reviewed by Duxbury.[8] The photochemical reactivity of triphenylmethane dyes is both complex and interesting and has captured the attention of many scientists. These dyes have been considered as promising candidates in textile industry because of their brilliant colors and high tinctorial strength. They are found to be useful in laser spectroscopy as saturable mode absorbers for mode locking, because of their low fluorescence yield and fast non-radiative decay.



Y, Z = H, OMe, OEt, Cl, Me_2N, Et_2N, OH, NHMe, NHEt, NH^tBu

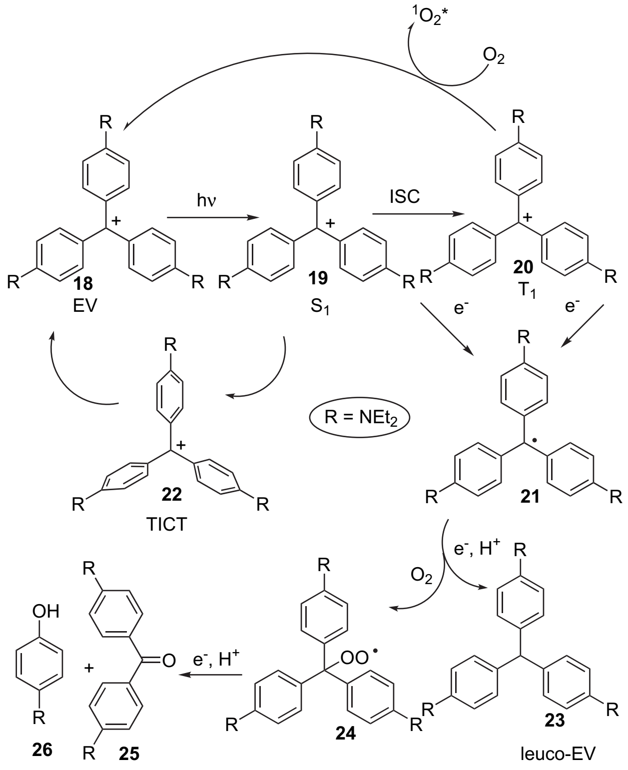
Scheme 3. (i) $+H^+$; (ii) $+OH^-$; (iii) $+RCH_2OH$, $-RCHO$; (iv) H_2O; (v) +HZ; (v′) +HY; (vi) $-H^+$; (vii) $+H^+$; (viii) $+NRH_2$; (ix) $-H^+$; (x) $+H^+$.

The TAM dyes exhibit interesting spectral features, consequent to their structure and their interaction with the physical and chemical environment (concentration of the dye, pH of the solution, pressure, temperature, variation in the counter anion etc.). It was found that such dyes show two types of absorption bands, viz. x- and y-band, where the x-band corresponds to the promotion of an electron from the nonbonding orbital to the lowest antibonding orbital, resulting in a high electron density on the central carbon atom, while the y-band arises from the excitation of an electron from the second highest occupied bonding orbital to the lowest vacant orbital.

The fluorescence lifetime of TAM dyes in a low-viscosity medium is typically in the picosecond range as a consequence of the fast relaxation process that occurs via rotational motions of the aryl rings.[19] In the context of the search for new sensitizers for photodynamic therapy, Baptista et al. have studied the effect of biological host bovine serum albumin (BSA) on Ethyl Violet (EV) fluorescence at 20 °C (pH~7.3).[20] The BSA binding sites were very efficient in preventing the free rotor motion in the dye, as indicated by an increment in EV fluorescence as a function of BSA concentration. It is observed that, in addition to a singlet and a triplet state, this process involves a twisted intermediate charge-transfer state (TICT). The proposed mechanism involves a two-electron process that can account for the formation of the products **23** and **25** (Scheme 4).

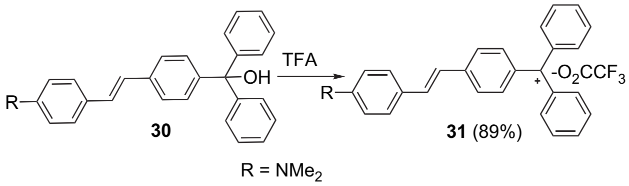
Sengupta et al. have used New Fuchsin (**27**), a cheap commercial dye for the synthesis of a tritolan dendron **29**, based on tetraphenylmethane scaffold (Scheme 5).[21] Energy transfer studies were carried out with the dendrimer **29**, in which the tolan part is the donor moiety and the anthracene core, the acceptor.

Screttas and co-workers synthesized a series of TAM dyes based on the stilbenyl group and, because these are nonlinear chromophores, such dyes exhibited second-order



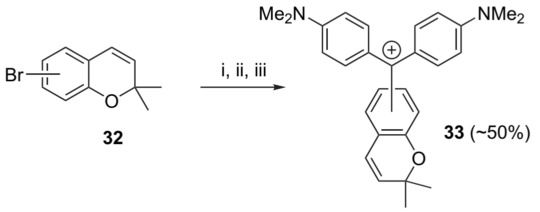
Scheme 4.

NLO properties.[22] Carbinols were obtained by the reaction of stilbenyllithium with ketones, ethyl benzoate or diethyl carbonate and the transformation into the corresponding cations was affected by dissolving the carbinols in TFA (Scheme 6).



Scheme 6.

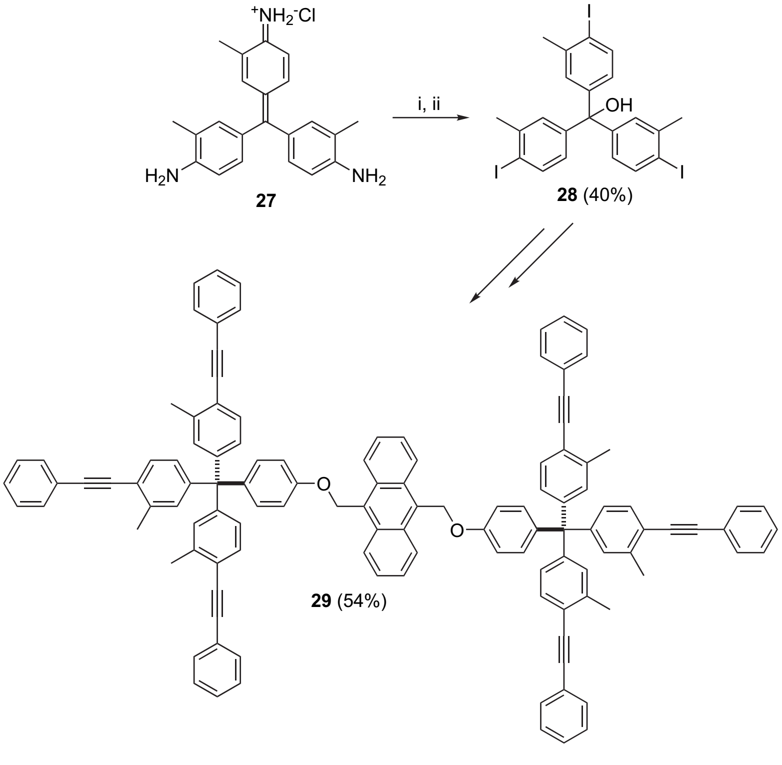
Clayton et al. have synthesized TAM dyes containing a 2*H*-1-benzopyran unit and the spectral parameters of these dyes were similar to that of the naphthyl derivative of Malachite Green.[23] Compound **33** was obtained by the reaction of lithiochromenes with 4,4′-bis(dimethylamino)benzophenone and subsequent treatment with acids (Scheme 7).



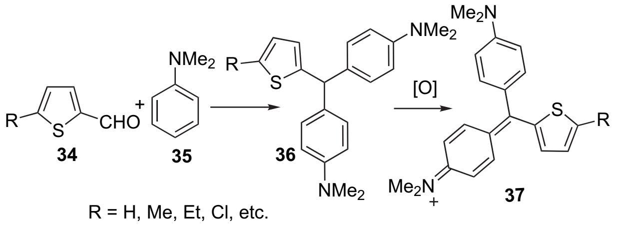
Scheme 7. (i) BuLi, TMEDA, Et_2O; (ii) $(4\text{-}NMe_2C_6H_4)_2CO$; (iii) H^+.

2.4. Heterocyclic dyes

The method for the synthesis of dyes incorporating heterocycles like thiophene involves the condensation of substituted thiophene aldehydes with dimethylaniline in the presence of anhydrous $ZnCl_2$, forming leuco-bases, which on oxidation afford the corresponding dyes (Scheme 8).[24,25]



Scheme 5. (i) Dil H_2SO_4, $NaNO_2$, 0 °C; (ii) KI, H_2O, rt.



Scheme 8.

The dyes could be isolated as crystals and the absorption spectra of such dyes also showed three principal bands, as in the case of the triphenylmethane dyes, viz. x-, y-, and x'-band. Substitution of the phenyl group of Malachite Green with thiophene shifts the y-band toward red, which may be attributed to the electron-releasing nature of the thiophene ring, compared to the phenyl ring. It was observed that, when the basicity of the nitrogen atoms increases, the absorption frequency is lowered. Dyes of the similar category containing thianaphthalene were also synthesized and investigated by Ghaisas and co-workers.[26] Thianaphthalene—Malachite Green also exhibited a similar bathochromic shift of the x-band.

2.5. Leucohydroxides and leucocyanides

By the use of suitable photocleavable compounds, the laser-induced pH jump technique can be used for the generation of a proton or hydroxide-ion pulse, which in turn, can be used for the study of chemical and biochemical processes. Triphenylmethane leuco-derivatives are well-known photochromic molecules, which dissociate into ion pairs under UV irradiation with the production of the intensely colored triphenylmethyl cation. Irie et al. have selected TAM leucohydroxide as the hydroxide-ion emitter in the laser-induced pH jump technique.[27,28] In order to overcome the insolubility in water, quaternary ammonium salts or sulfonate groups were introduced on the molecule (Fig. 4). On irradiation, the pH of the solution increased, because of the ejection of hydroxide ions from the excited TAM leucohydroxide.

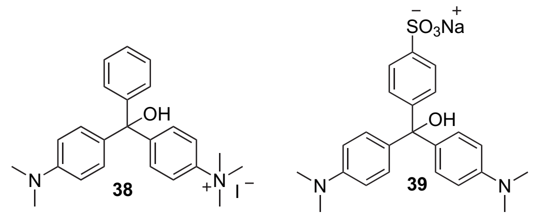
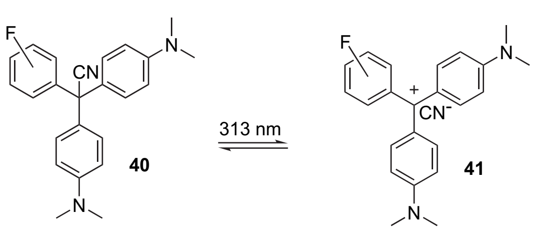


Figure 4.

Holmes showed that photoionization of the leucocyanides of Malachite Green, Crystal Violet, and Sunset Orange occurs only in a solvent with high dielectric constant.[29] Non-acid-sensitive color formers for photochemically cured, cationic polymers were developed by Malpert et al. by making use of the fact that the leuconitriles undergo heterolytic cleavage of the cyanide moiety upon irradiation with UV light, forming the colored cation (Scheme 9).[30] By suitably controlling the concentration or by changing the irradiation dose, leaving the substituents on the phenyl ring anionic, it is possible to tune the color formation.[31] The effect of ring fluorination on the absorption spectrum of Malachite Green was investigated by Hallas et al.[32]



Scheme 9.

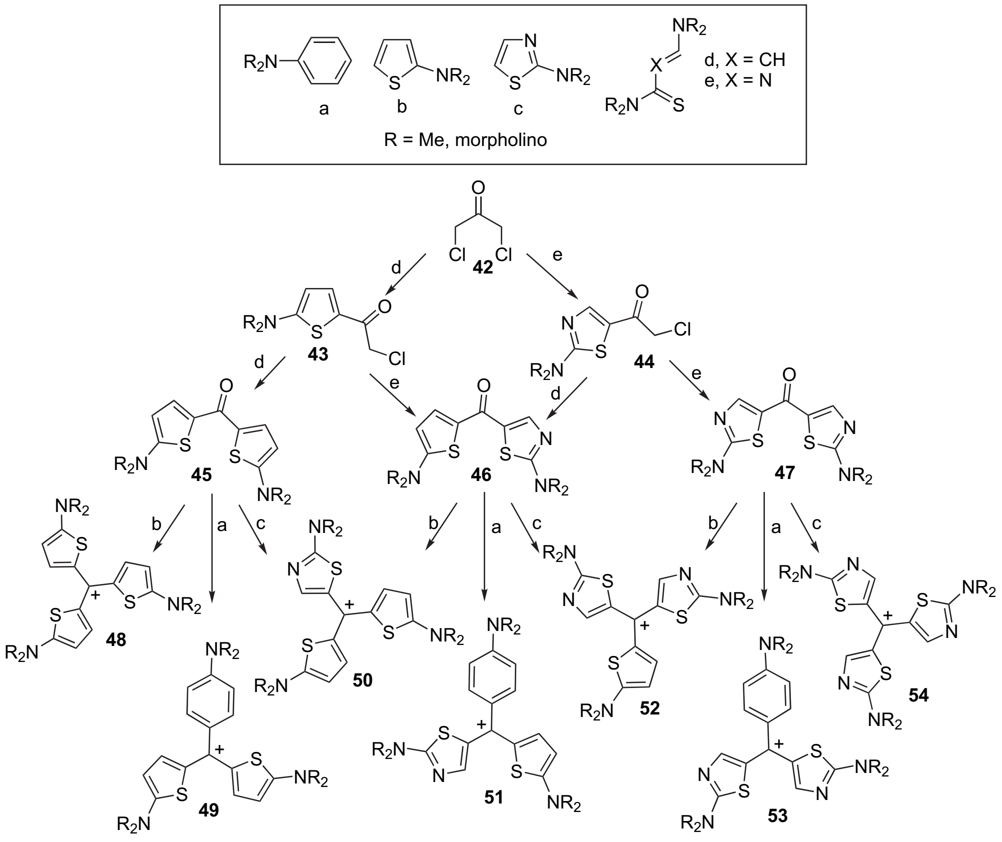
Recently, Noack et al. have shown that the heterocyclic analog of Michler's ketone could be efficiently employed for the synthesis of various heterocyclic Crystal Violet dyes (**48–54**, Scheme 10) and, according to theoretical studies, these molecules should display special NLO behavior.[33]

2.6. Triarylmethanol derivatives

Triarylmethanol derivatives were studied extensively because of their photocleavable nature, which gives an intense color change on irradiation by UV–vis light, both in polar solvents and in the solid state.[26,34,35] The clathrate-forming property of triarylmethanol derivatives with solvents like acetone, methanol, DMSO, dioxane, etc. is deemed to have application involving the concentration, separation, and purification of such solvents from industrial and environmental solutions and vapors.[36,37] Triarylsilanol derivatives also possess such inclusion properties.[38,39] Hayashi et al. have demonstrated that fluorine-substituted triarylmethanols exhibit properties different from those of the unsubstituted compounds because of the intermolecular $C–F\cdots\pi$ interaction, which controls the structural packing motif and the thermal stability of the crystal through crystal structures.[40]

Bacchi et al. have used the diol derivatives of general formula $HOC–(Ar_2)–L–(Ar_2)–COH$, where L is a suitable spacer, for the development of 'wheel-and-axle' systems (Fig. 5) utilizing the clathrating property of the triarylmethanols.[41] They showed that, by introducing a metal center into the spacer, the coordination of the metal at the peripheral region of the TAM molecules could control the electronic properties of the chromophore. They selected $Ag(LOH)_2(OTf)(MeCN)$, which was prepared by reacting LOH with excess Ag(OTf). It was shown that the metal is coordinated to two pyridine rings of the LOH group and two OH groups are connected through the SO_2 group via hydrogen bonding ($OH\cdots O–S–O\cdots HO$).

Gibson et al. have shown that alcohol-, halide-, phenol-, aniline-, and carboxylic acid-functionalized TAM can serve as blocking end units in rotaxanes and polyrotaxanes.[42] Two different approaches were employed for the introduction of the spacer into various TAM derivatives. In the first approach via a carbanion, the carbinols were reduced to TAM quantitatively and the anions generated with *n*-butyllithium were alkylated with chloro-alcohols, affording the ω,ω,ω-triarylalcohols. In the second approach, the triarylmethyl cation derived from the triarylcarbinol or the chloride was subjected to electrophilic substitution reactions with phenols and aniline (Scheme 11).



Scheme 10.

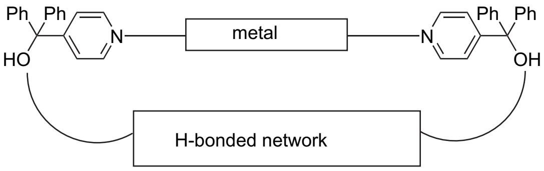
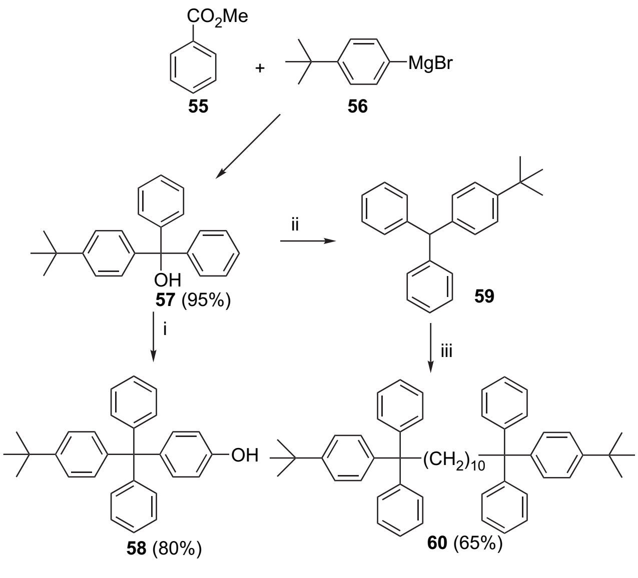


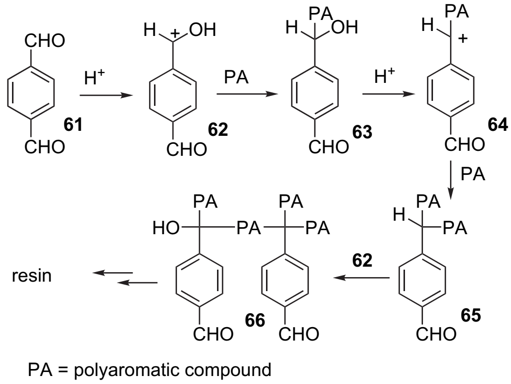
Figure 5.



Scheme 11. (i) H^+, phenol; (ii) HCO_2H; (iii) *n*-BuLi; $Br(CH_2)_{10}Br$.

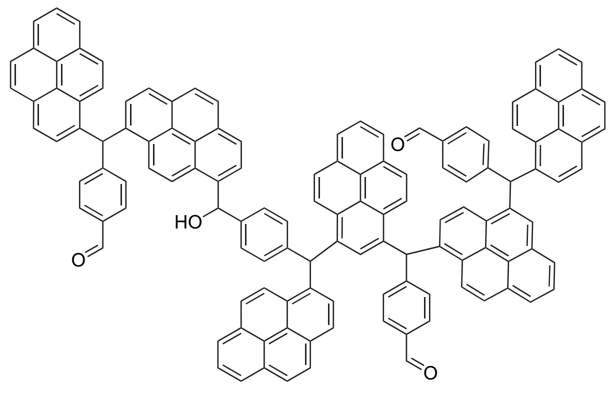
2.7. TAM in polymer chemistry

Ota's group has developed a thermosetting condensed polynuclear aromatic (COPNA) resin composed of a TAM structure by heating a mixture of a polycyclic aromatic compound and an aromatic aldehyde in the presence of an acid catalyst, as shown in Scheme 12.[43]



Scheme 12.

When the synthesis was carried out in a magnetic field, the resulting resin exhibited ferromagnetic properties with excellent reproducibility.[44] For instance, compound **66′** in Figure 6, which has ferromagnetic properties, was synthesized by heating a mixture of terephthalaldehyde and pyrene with 5 wt % of PTSA at 130–140 °C under a magnetic field of 440 G for 1 h.



66'

Figure 6.

Polymeric Malachite Green derivatives show complexing ability toward K^+, Cs^+, Li^+, and Na^+ ions and it has been shown that the complexation can be controlled photochemically.[45] Bis-crowned Malachite Green copolymers with styrene and methyl methacrylate as co-monomers and *N*,*N*-dimethylacrylamide and 4-hydroxymethylstyrene as hydrophobic co-monomers were synthesized and studied with respect to their metal-ion-complexing ability. The properties of the polymer having a bis-crowned Malachite Green moiety exhibited a substantial difference from the corresponding monomeric analog. The decoloration reaction of the photocationic form was found to be governed by the rheology of the polymer in solution.[46]

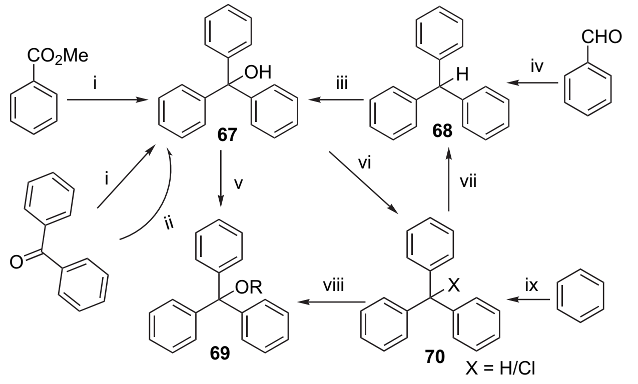
2.8. Miscellaneous

In addition to the applications mentioned above, the trityl group serves as an excellent protective group used in nucleoside, oligonucleoside, peptide, and carbohydrate chemistry.[47] Trityl groups are utilized in multistep syntheses on solid phase, mostly as linkers, and they have found application in medicinal chemistry. Prodrugs with trityl-protected nucleosides were developed and their site-selective delivery was tested in vivo against tumor cells.[48] Because of their easy-ionizing properties, trityl cations can additionally act as a tool for mass-spectrometric analysis.[49]

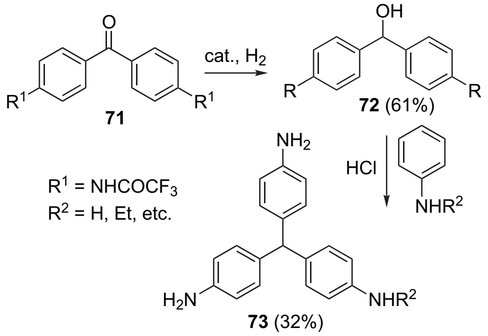
2.9. Synthesis

Two basic approaches to trityl synthesis are (i) the Grignard reaction of various carbonyl compounds like benzophenone, methyl benzoate, etc. and (ii) the aromatic electrophilic substitution reaction in acidic media.[3,50] The alcohol can either be converted into the halogenated compound or into the alkyl ether. Symmetric TAMs were prepared by the treatment of electrophilic reagents such as triethyl orthoformate or chloroform with arene nucleophiles (Scheme 13).[51]

Panda and co-workers have recently reported an efficient synthesis of unsymmetrical triarylmethanes by Friedel–Crafts reaction of aromatic nucleophiles with heteroaryl carbinols.[52] Werbel et al. have reported a facile method for the synthesis of triarylmethane **73** by the catalytic hydrogenation of the diaryl ketone **71** and the subsequent treatment of the carbinol with aryl amines and HCl (Scheme 14).[53]

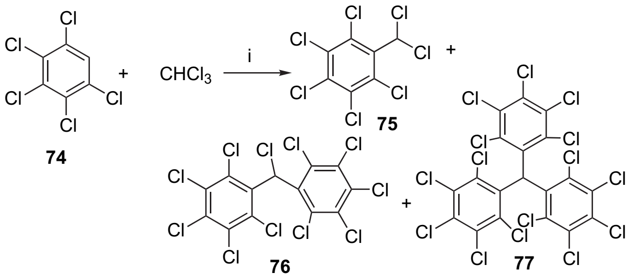


Scheme 13. (i) PhMgBr, (ii) BuLi, bromobenzene; (iii) PbO/$MeCO_2H$, DDO; (iv) $MeCO_2H$, H_2SO_4, benzene; (v) ROH/H^+; (vi) RCOX; (vii) R_2NLi; (viii) ROH/base; (ix) $CCl_3X/AlCl_3$(R=alkyl).



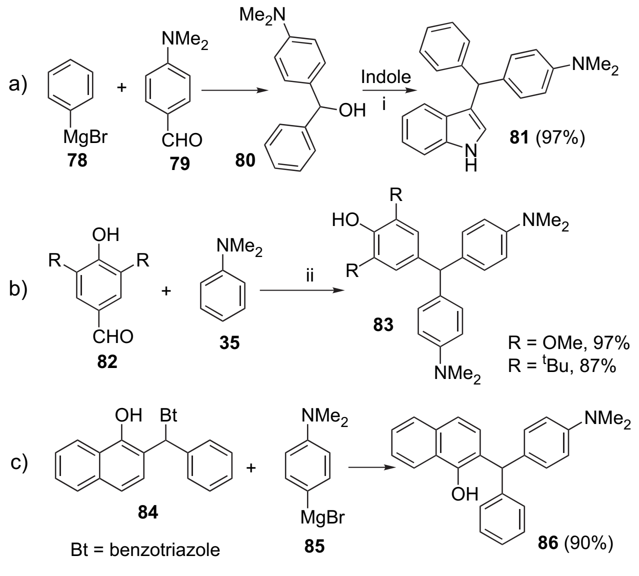
Scheme 14.

A simple, direct, and high-yielding Friedel–Crafts synthesis of highly chlorinated aryl-, diaryl-, and triarylmethanes was reported by Ballaster et al.[54] This involves the condensation reaction between chloroform and the chlorinated benzene, affected using $AlCl_3$ at a temperature ranging from 70 to 150 °C (Scheme 15). It was observed that, according to the amount of halogenated benzene, yields of the products varied. Compounds like **76** and **77** are valuable chemical precursors of inert free radicals.



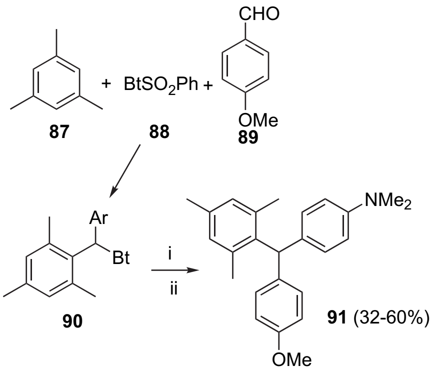
Scheme 15. (i) $AlCl_3$, 70–150 °C.

Katritzky et al. have developed three synthetic routes to access asymmetric TAM: (a) reaction of a benzhydrol with an electron-rich aromatic compound, (b) direct condensation of an aromatic aldehyde with electron-rich arenes, and (c) displacement of benzotriazolyl derivatives by Grignard reagents (Scheme 16).[55]



Scheme 16. (i) Concd HCl, H_2O/MeOH; (ii) concd H_2SO_4, urea, 90 °C.

Recently, a combination of 1-benzenesulfonyl benzotriazole and an aromatic aldehyde has been used in a new protocol for the synthesis of asymmetric TAM (Scheme 17).[56]

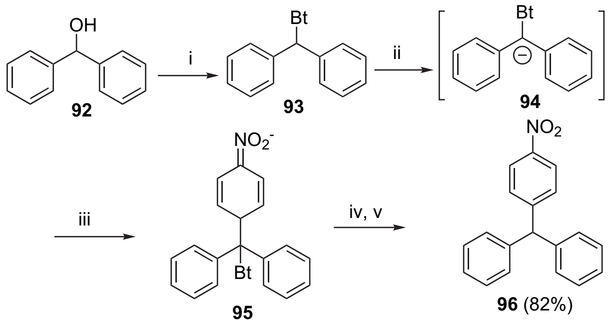


Scheme 17. (i) *N*,*N*-Dimethylaniline; (ii) $ZnCl_2$, CH_2Cl_2.

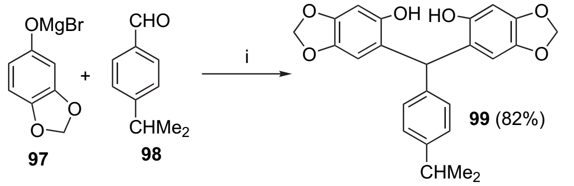
Katritzky's group has reported the synthesis of (*p*-nitroaryl)-diarylmethane, a compound, which has attracted attention because of the easy reduction of the nitro group to an amino group and its subsequent transformations. In this new method, diarylmethanols were treated with benzotriazole under acid catalysis in the presence of perfluorocarbon fluids and, subsequently, with nitrobenzene.[57] Diarylmethylbenzotriazoles are highly nucleophilic in the presence of strong bases and hence react with electron-poor arenes efficiently (Scheme 18).

The selective condensation of oxophilic metal phenolates with an aromatic aldehyde at the *ortho* position of the starting phenol has been utilized in the synthesis of a 2,2′-dihydroxytriphenylmethane, another TAM derivative (Scheme 19).[58]

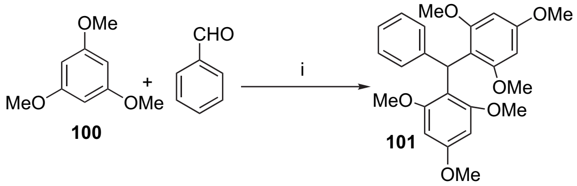
Recently, we have shown that electron-rich arenes can be efficiently condensed with aldehydes under the catalytic influence of $AuCl_3$/AgOTf (Scheme 20).[59]



Scheme 18. (i) BtH; (ii) *t*-BuOK; (iii) nitrobenzene; (iv) *t*-BuOK; (v) H^+.

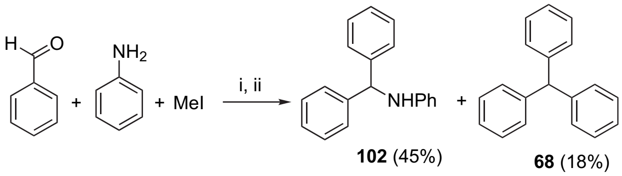


Scheme 19. (i) CH_2Cl_2, reflux.



Scheme 20. (i) 1 mol % [$AuCl_3$/3AgOTf], MeCN, argon, 50 °C, 85%.

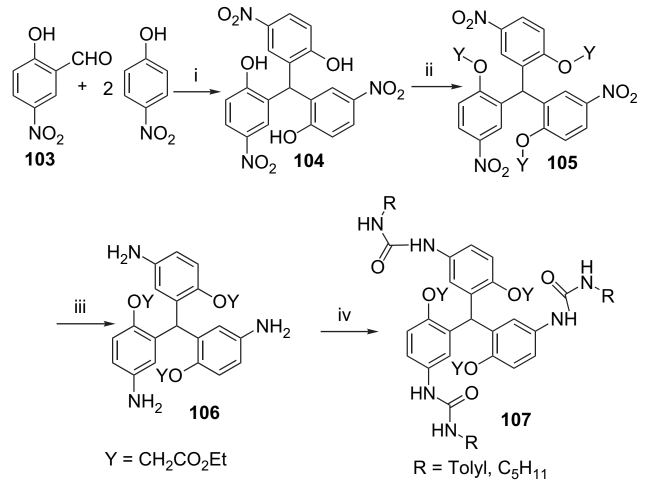
Triarylmethanes are formed, albeit in low yields, in the alkyl radical addition to a mixture of ketone and aniline (Scheme 21).[60]



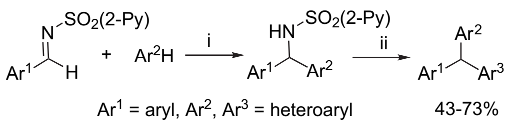
Scheme 21. (i) PhN_2^+, Ti(III); (ii) H^+, H_2O.

Tri-(2-alkoxy-5-ureido-phenyl)methanes were prepared by the acid-catalyzed condensation of 2-hydroxy-5-nitro-benzaldehyde with a two-fold excess of *p*-nitrophenol. The product was *O*-alkylated and subsequent reduction of the nitro group by catalytic hydrogenation and amidation led to the compound **107** (Scheme 22). A single-crystal X-ray analysis of the compound **106** showed that it had a three-bladed propeller conformation in which both the *O*-alkyl group and the amide functionality were found in a *syn* arrangement relative to each other.[61]

Esquivias et al. have recently reported an efficient synthesis of di- and triarylmethanes involving an aza-Friedel–Crafts reaction of *N*-(2-pyridyl)sulfonyl aldimines catalyzed by a $Cu(OTf)_2$/binap system (Scheme 23).[62]



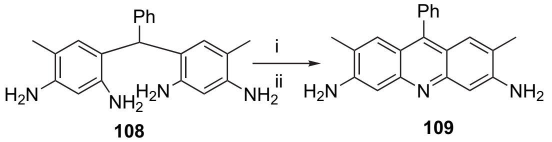
Scheme 22. (i) H_2SO_4, 155 °C; (ii) YBr, K_2CO_3, acetone; (iii) H_2, Raney-Ni, THF/EtOH; (iv) RNCO, CH_2Cl_2.



Scheme 23. (i) $Cu(OTf)_2$ (10 mol %), (±) binap (10 mol %), CH_2Cl_2, reflux; (ii) Ar^3H, 40 °C, 20–120 min.

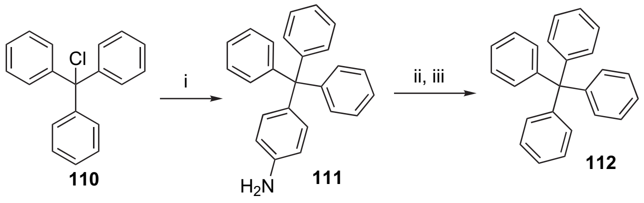
2.10. Reactions of TAM derivatives

Snyder and Konecky have demonstrated that tetraaminoaryl compounds like **108** undergo cyclization and subsequent aromatization to diaminoacridine derivative **109** on treatment with polyphosphoric acid at 165 °C (Scheme 24).[63]



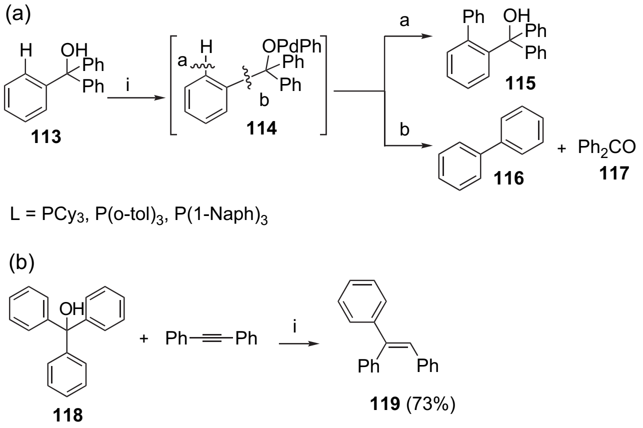
Scheme 24. (i) PPA, 165 °C; (ii) NaOH.

Zimmermann et al. have synthesized tetraphenylmethane by the condensation of triphenylmethyl chloride and aniline, followed by reductive elimination via diazotization and subsequent reduction of the azo compound (Scheme 25).[64]



Scheme 25. (i) Aniline, 220 °C, neat; (ii) H_2SO_4, $C_5H_{11}ONO$, DMF; (iii) aq H_3PO_2.

Terao et al. have shown that a number of α,α-disubstituted arylmethanols react with aryl halides in the presence of palladium acetate to give biaryls. The reaction proceeds through a Pd(II) alcoholate intermediate **114**, which on β-carbon elimination, furnishes the product (path b in Scheme 26). A competitive reaction is the *o*-C–H bond cleavage of the triarylmethanols (path a in Scheme 26). It has been revealed that hydroarylation of some unsaturated compounds like alkynes or α,β-unsaturated compounds occurred when $P(1\text{-}Naph)_3$ is employed as the ligand in this reaction.[65] This reaction may also be utilized as a method for the deprotection of diaryl ketones.



Scheme 26. (a) (i) $Pd(OAc)_2$, L, PhBr, Cs_2CO_3; (b) (i) $Pd(OAc)_2$, $P(1\text{-}Naph)_3$, PhBr, Cs_2CO_3.

2.11. Stereochemistry

Finocchiaro et al. have separated two diastereomers of the TAM of the type Ar_3Z (e.g., compound **120**, Fig. 7) with three different aryl groups lacking C_2 axes. The compound was prepared by the condensation reaction of 1-(2-methoxynaphthyl)-1-(2-methylnaphthyl)methanol and 2,4,6-trimethoxytoluene in nitromethane with H_2SO_4 as the catalyst. The interconversion between the two forms is due to a one-ring-flip mechanism.[66] Variable temperature NMR studies also confirmed the presence of the diastereomers.

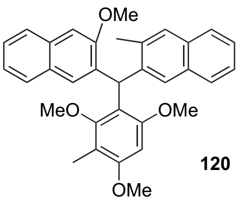


Figure 7.

3. Symmetric triheteroarylmethanes

3.1. Tri-2-thienylmethane

In the context of the wide-ranging applications of triphenylmethyl derivatives,[47] triheteroarylmethanes like tri-2-thienylmethane **121** (Fig. 8), have attracted the attention of several chemists because of their potential applications. The thiophene derivative is expected to have wider applications in view of the ease of functionalization of thiophene at the C-2 position by either an electrophilic substitution reaction or lithiation followed by reaction with electrophiles. The potential use of thiophene as a synthon equivalent of *n*-butane via Raney-nickel reduction is also noteworthy.

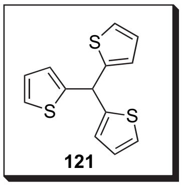


Figure 8.

Noack et al. have synthesized several heterocyclic analogs of the trityl cation containing thiophene and thiazole rings.[67] For application in non-linear optics and conducting polymers, a series of thienylic and oligothienylic trityl analogs was prepared.[68]

3.1.1. Trithienylmethyl radicals. Although the triphenylmethyl radical had been known since 1900, its heterocyclic analogs were brought to light only in 1968, by the detection of tri-2-thienyl- and tri-3-thienylmethyl radicals **122** and **123**, respectively (Fig. 9).[69]

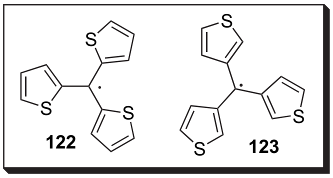


Figure 9.

Bernardi et al. have carried out an INDO study on the tri-2-thienylmethyl radical, which proved that the radical exists as a pair of diastereomeric conformers, a cis form with C_3 symmetry and a trans form with C_1 symmetry, as shown in Figure 10.[70]

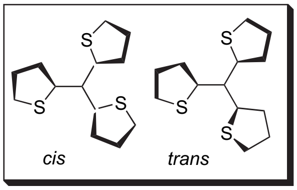
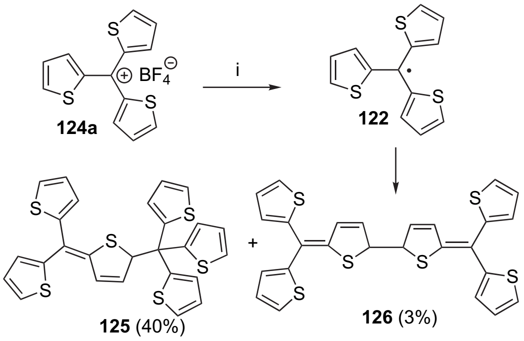


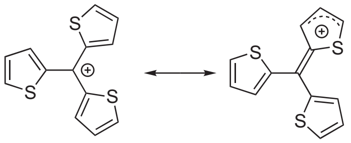
Figure 10.

No structural proposal for the dimer of the tri-2-thienylmethyl radical was attempted until Nakayama et al. carried out some investigations on the dimerization of the radical in 1990. They reported the formation, structure elucidation, and interconversion of the two isomeric dimers of **124a** (Scheme 27).[71] Based on extensive studies, the authors have concluded that the dimerization of the radical between the radical center and the sterically less-hindered 5-position of the 2-thienyl ring initially afforded the kinetically favored product **125**, which then thermally equilibrated to another dimer **126**.

3.1.2. Tri-2-thienylmethyl cation and tri-2-thienylmethyl anion. Taddei et al. in 1970 reported the proton NMR spectral parameters for the isomeric trithienylcarbenium ions,[72] while their ^{13}C NMR characteristics were investigated in some detail by Abarca et al. (Scheme 28).[73]

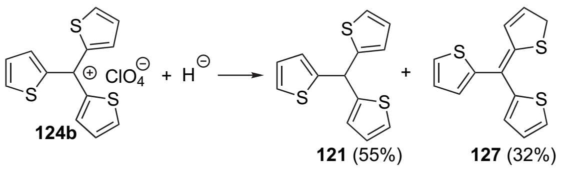


Scheme 27. (i) Zn, DME, 65 °C.



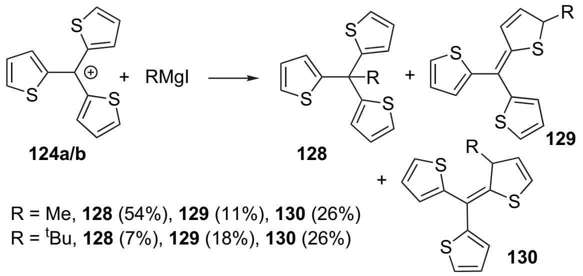
Scheme 28.

The reactivity profile of the carbenium ion toward hydride and carbon nucleophiles was studied by Ishii et al. and it was observed that addition occurs not only at the carbenium ion center, but also on the thiophene ring.[74] Thus, the addition of LAH to an ethereal solution of tri-2-thienylcarbenium perchlorate **124b** at room temperature results in rapid hydride addition, both at the carbenium ion center and at the 5-position of the thiophene ring, affording the compounds **121** and **127** (Scheme 29).



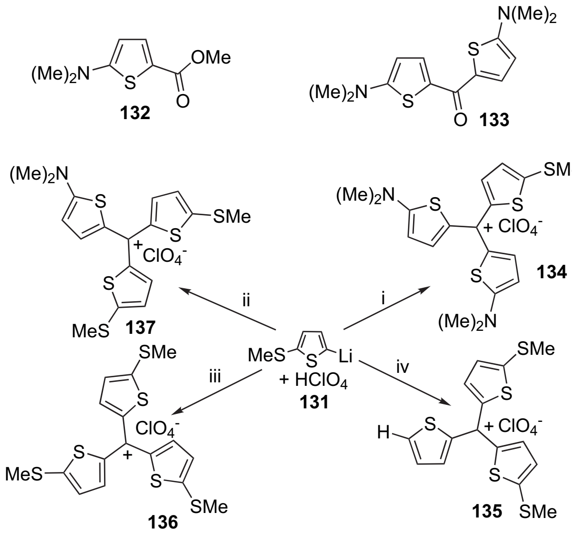
Scheme 29.

In order to understand the reaction of carbon nucleophiles toward **124**, a variety of organometallic reagents have been employed. This reaction, giving rise to compounds **128**, **129**, and **130**, is illustrated in Scheme 30. As the alkyl group becomes bulky, addition at the central carbon becomes less prominent.



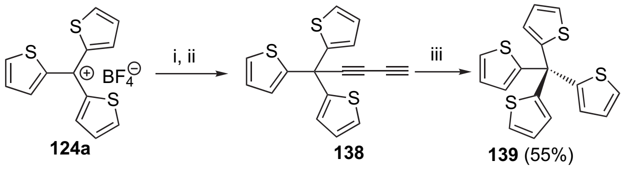
Scheme 30.

Deeply colored 5-methylmercapto- and 5-methylamino-substituted tri-2-thienylmethinium perchlorates **134–137** were prepared by the reaction of 2-methylmercapto-5-lithiothiophene **131** with methyl 2-dimethylamino-5-thiophenecarboxylate **132**, bis(2-dimethylaminothiophen-5-yl)ketone **133** or diethyl carbonate and perchloric acid (Scheme 31).[75]



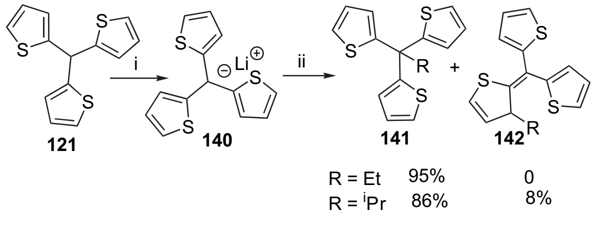
Scheme 31. (i) **133**; (ii) **132**; (iii) $(EtO)_2CO$; (iv) $C_4H_3SCO_2Me$.

The synthetically and structurally important molecule, tetrakis(2-thienyl)methane **139**, was synthesized for the first time by Matsumoto et al. using sodium sulfide-induced cyclization of 5,5,5-tri-2-thienylpentadiyne **138**, which in turn, was obtained from tri-2-thienylmethyl cation **124a** (Scheme 32).[76]



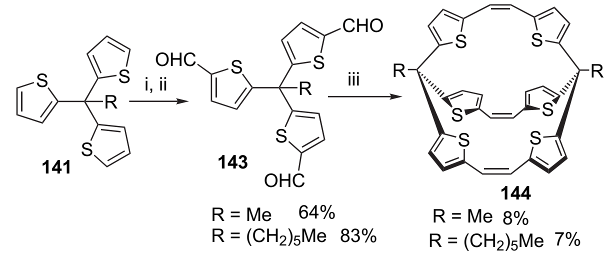
Scheme 32. (i) Li—≡—≡—TMS; (ii) K_2CO_3, MeOH; (iii) Na_2S–NaOH, DMSO, 120 °C.

Nakayama et al. explored the reactivity of the corresponding anion, the tri-2-thienylmethyl anion **140**, toward carbon electrophiles.[77] They found that the optimum conditions for addition of electrophiles to the methine carbon involve the use of butyllithium (1.3 equiv) in the presence of TMEDA (1.5 equiv) in THF at −78 °C and subsequent addition of excess alkyl halide (5 equiv) to the red suspension of the anion formed (Scheme 33). Although the reaction of the tri-2-thienylmethyl anion with primary alkyl halides occurs exclusively at the carbanion center, its reaction with bulkier secondary and tertiary alkyl halides occurs both at the carbanion center and at the less-hindered thiophene ring.



Scheme 33. (i) BuLi, TMEDA, THF, −78 °C; (ii) RBr.

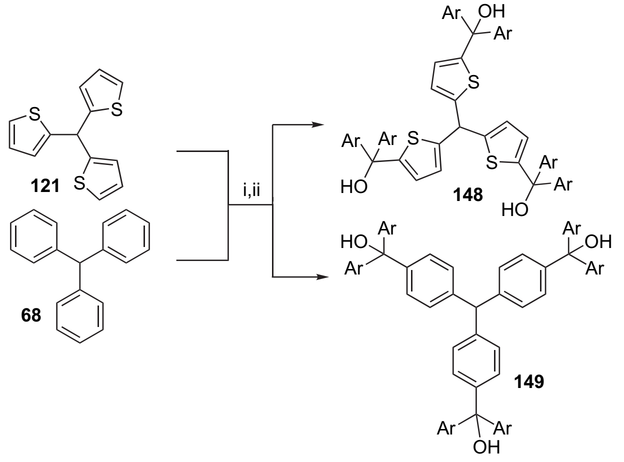
The synthesis of cage molecules (e.g., compound **144**, Scheme 34) bicapped with tri-2-thienylmethane was achieved by Kurata et al. in 2001.[78] The target molecule was obtained via a McMurry coupling reaction of tri-5-formyl-2-thienylmethanes. All the sulfur atoms of the six thienyl groups are directed inwards and, hence, the molecule has a three-dimensional cavity, which can potentially encapsulate metal ions.



Scheme 34. (i) BuLi-THF, 0 °C; (ii) excess DMF; (iii) $TiCl_4$, Zn, CuI-DME, rt.

Compound **144** on further reaction led to the formation of the cage-molecular monocation **145**, dication **146**, and dianion **147** of substantial stability, the first examples of fully conjugated ionic cyclophane cage molecules (Fig. 11).[79]

Oda et al. have synthesized hexaaryl-substituted trimethylenemethane dications and dianions extended with thiophene or benzene, which in turn, were prepared from the corresponding alcohols (Scheme 35).[80] These molecules have tetrapolar properties and long-wavelength absorption in the near-IR region. Thiophene-extended dications and dianions are stable, compared to benzene-extended dications, the latter being sensitive to acids.



Scheme 35. (i) LDA, Ar_2CO; (ii) H_2SO_4.

The dications were prepared by dissolving the alcohols **148** or **149** in CF_3CO_2H and a detailed NMR study revealed that the dication has tetrapolar properties. The corresponding

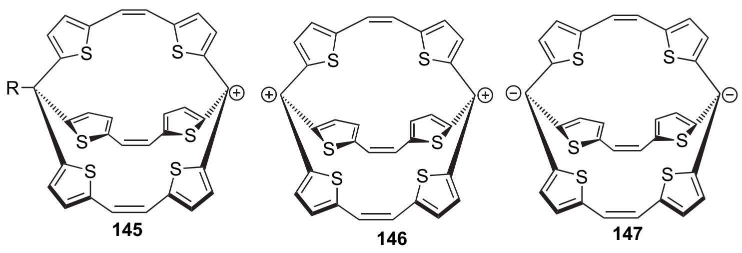
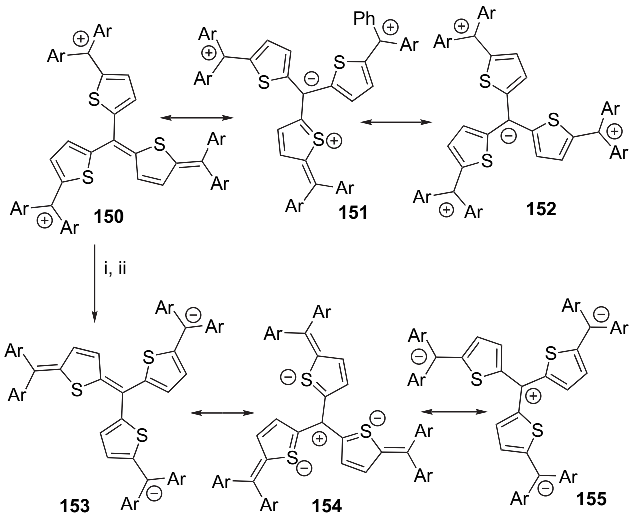


Figure 11.

anion was obtained from the dication by LAH reduction, followed by deprotonation using NaH (Scheme 36).



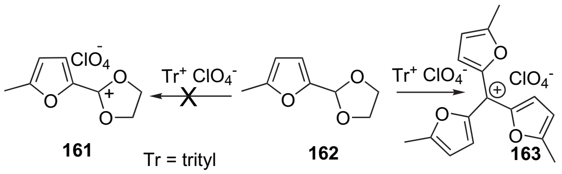
Scheme 36. (i) LAH; (ii) NaH, DMSO.

3.1.3. Electrophilic substitution reactions. Investigations by our group have shown that tri-2-thienylmethane underwent electrophilic substitution reactions such as Friedel–Crafts reaction, formylation reaction, bromination, and reactions with electrophilic carbenes (Scheme 37).[81]

3.2. Tri-2-furylmethane

Conventional methods for the synthesis of symmetric tri-2-furylmethanes consist of the condensation of 2-furaldehyde with the corresponding furan substrates or the reaction between furan compounds and chloroform.[82]

During the synthesis of the dioxolanium salt **161** from 2-[5-methylfur-2-yl]-1,3-dioxolane **162**, accidentally, Stroganova et al. have observed the formation of trifurylcarbenium perchlorate **163** in trace amounts (Scheme 38).[83]

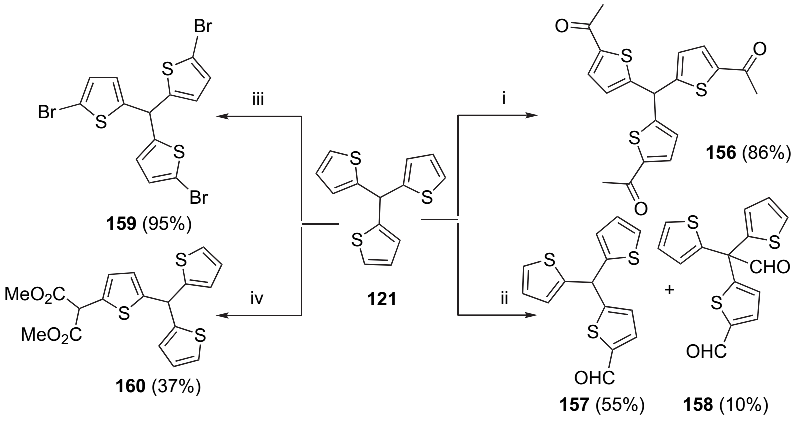


Scheme 38.

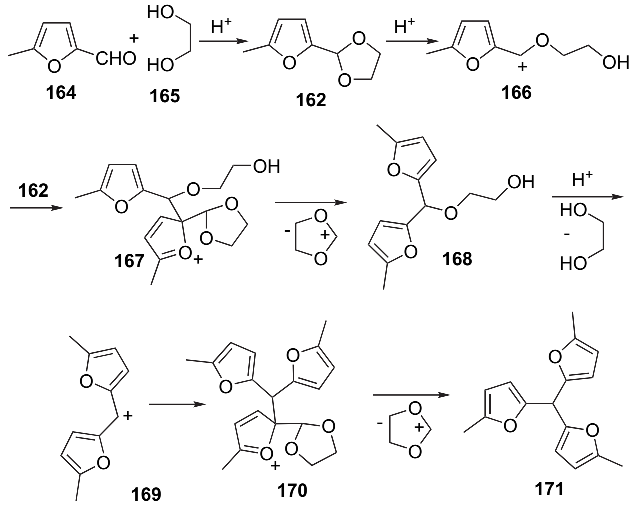
The probable mechanism for the formation of the product is shown in Scheme 39. In another attempt, Riad et al. have synthesized tri-2-furylmethane by the condensation of furfural with furan using macroporous ion-exchange resins as catalysts.[84]

The influence of various acid catalysts on the selectivity of the reaction of furfural and ethylene glycol has been studied and it was concluded from the experimental observations that weakly acidic catalysts like ion-exchange resins favor the formation of the dioxolane **162**, while strong catalysts favor the formation of the trifurylmethane **171** (Scheme 40).

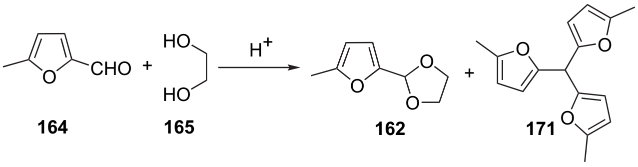
A similar strategy was employed for the synthesis of tri-(5-aryl-2-furyl)methanes **173**, which is important because of the fact that 2-arylfurans are not easily accessible by traditional methods (Scheme 41).



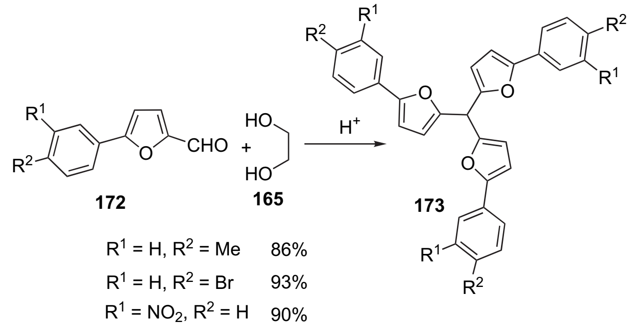
Scheme 37. (i) MeCOCl, $AlCl_3$; (ii) DMF, $POCl_3$; (iii) NBS; (iv) $(CO_2Me)_2CN_2$, Rh(II).



Scheme 39.

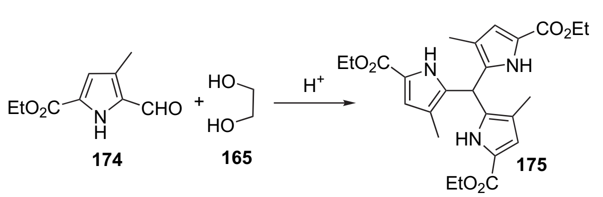


Scheme 40.



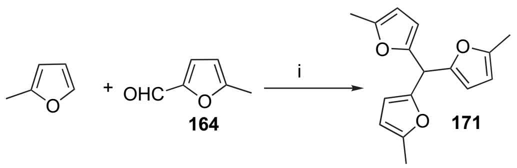
Scheme 41.

A similar conversion of a pyrrolic aldehyde is also known. When the pyrrolic aldehyde **174** was treated with ethylene glycol in the presence of catalytic amount of *p*-TsOH, the product obtained was tripyrrolylmethane **175**, instead of the expected acetal (Scheme 42).[85]



Scheme 42.

A gold(III) chloride-promoted condensation can be effectively utilized for the synthesis of a range of symmetrical and unsymmetrical triheteroarylmethanes.[59] Thus, tri(5-methylfur-2-yl)methane **171** was obtained in 90% yield by the condensation of 2-methylfuran with the corresponding aldehyde in presence of $AuCl_3$ (Scheme 43).



Scheme 43. (i) $AuCl_3$ (1 mol %), MeCN, argon, rt, 12 h, 93%.

Other heterocycles like indole, 2-methylthiophene, etc. also reacted efficiently under the above reaction conditions. A high-yield synthesis of complex molecules like **176** in one pot has been accomplished by the participation of poly-aldehydic substrates in this reaction (Fig. 12).

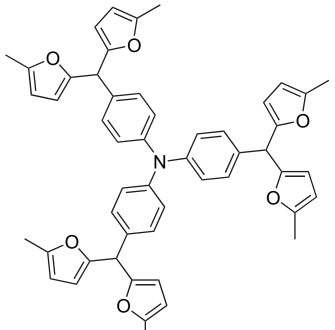
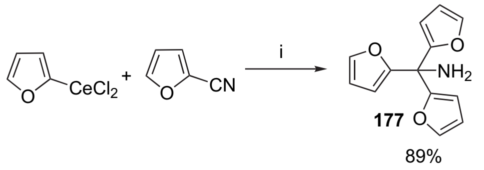

176

Figure 12.

Ciganek has reported the preparation of tri-2-furylmethylamine **177**, via the cerium-mediated addition to 2-cyanofuran (Scheme 44).[86]

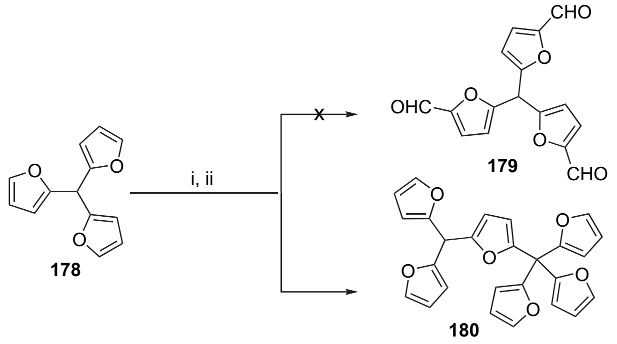


Scheme 44. (i) THF, −65 °C—rt.

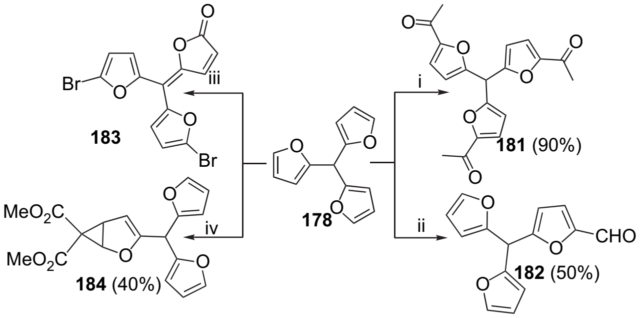
3.2.1. Reactions of tri-2-furylmethane.

In an experiment designed to synthesize a trisaldehyde of tri-2-furylmethane, serendipitously we observed the formation of 1,1-bisfuryl-1-[5-(tri-2-furylmethyl)]furylmethane **180**, a dimer of the tri-2-furylmethane radical (Scheme 45).[87]

The reactivity of tri-2-furylmethane **178** toward a number of electrophilic reagents was investigated in detail. A Friedel–Crafts reaction on **178** afforded the tris-acetylated compound **181**, while formylation gave only monoaddition. Bromination with NBS under different conditions afforded the butenolide **183** with two bromofuran substituents. Reaction of **178** with electrophilic carbenes yielded cyclopropanated and α-substituted products. Similarly, attempts toward the synthesis of tri-2-furylmethyl bromide resulted in the formation of the furanone derivative **183** (Scheme 46).[81]



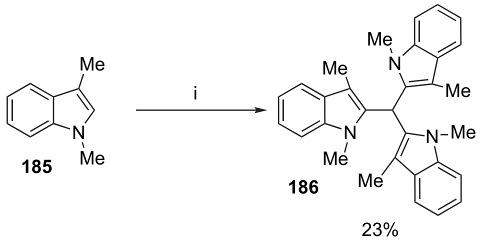
Scheme 45. (i) BuLi, TMEDA, THF, −78 °C; (ii) DMF.



Scheme 46. (i) MeCOCl, $AlCl_3$; (ii) DMF, $POCl_3$; (iii) NBS; (iv) $(CO_2Me)_2CN_2$, Rh(II).

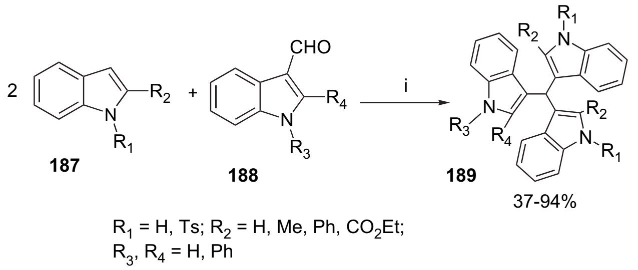
3.3. Triindolylmethane

Triindolylmethanes were usually prepared by the reaction of indoles with the corresponding aldehyde or with triethyl orthoformate.[88–90] Avendano et al. have synthesized tris-[(1,3-dimethyl)-2-indolyl]methanol by the reaction of the 2-lithio derivative of 1,3-dimethylindole with diethyl carbonate (Scheme 47).[91]



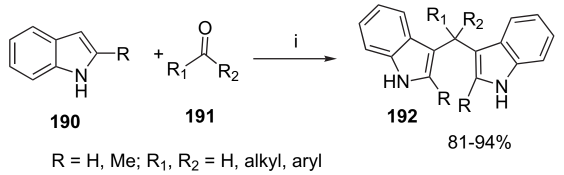
Scheme 47. (i) BuLi, $(EtO)_2CO$.

Chakrabarty et al. have developed a clay-mediated eco-friendly route toward symmetrical and unsymmetrical triindolylmethanes.[92,93] Recently, Jun et al. have shown that solid acids would also catalyze the condensation reaction efficiently.[94] A high-yield synthesis of triindolylmethanes as well as their *N*-acetyl derivatives was reported by Li et al. The reaction involved treatment of indoles with indole aldehydes in presence of acetic acid and acetic anhydride (Scheme 48).[95] The cytotoxic properties of these compounds were also reported by the same authors.



Scheme 48. (i) $MeCO_2H$, $(MeCO)_2O$.

Cerium(IV) ammonium nitrate has been shown to be an efficient catalyst for the synthesis of di- and triindolylmethanes in high yields (Scheme 49).[96]



Scheme 49. (i) CAN, MeCN, rt.

Triindolylmethane with trityl perchlorate or $FeCl_3$ oxidation gave the corresponding triindolyl cation, which was reversibly converted into the carbinol by treatment with alkali.[97,98] Because of the steric bulk and heterocyclic nature, 2,2′,2″-triindolylmethane was used as a good ligand for monometallic complexation, which in turn, would increase the Lewis acidity at the metal centers.[99]

4. Conclusions

Triaryl- and triheteroarylmethanes have found wide-ranging applications in different areas of chemistry. The classical dyestuff chemistry relies mainly on the triarylmethyl core, whereas the trityl group represents an important protective group for a range of functionalities. The medicinal applications of TAM derivatives are also well documented. Again, the photolabile nature of TAM leuco-derivatives made them useful in many photodevices. The present report gives an overview of the major synthetic routes to TAM derivatives, along with an account of their potential applications and reactions. From the ongoing discussion, it is clear that the chemistry of triaryl- and triheteroarylmethanes is witnessing a rapid growth. The development of novel synthetic methodologies enabling higher conversions under mild reaction conditions will definitely provide an added momentum to research in this area. It is anticipated that the present report will attract the attention of many scientists toward the potential applications of triaryl- and triheteroarylmethanes and will lead to important developments in this area.

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