Tetrahedron Letters 51 (2010) 4429–4432

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

meta-Substituted triphenylamines as new dyes displaying exceptionally large Stokes shifts

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ARTICLE INFO

Article history:
Received 7 May 2010
Revised 14 June 2010
Accepted 16 June 2010
Available online 20 June 2010

Keywords:
Triphenylamines
Fluorescence
Stokes shift

ABSTRACT

A straightforward synthesis of fluorescent tris-*meta*-substituted triphenylamines (*m*-TPAs) is presented. These new fluorophores display a unique feature that is a remarkably high Stokes shift up to 250 nm, as compared to their *para* counterparts. Although the *meta* substitution is made at the expense of the quantum yield, the latter is maintained at an appreciable level (5%) making the *m*-TPAs a new class of fluorophores adaptable to a large range of applications from biology to materials science.

Rapid development of fluorescence imaging and microscopy technologies in recent years has stimulated the emergence of sophisticated new fluorescent dyes displaying specific advantages including high quantum yield (Φ_F), high photostability, long lifetime, excimer formation, biocompatibility, chemical conjugability, etc.

However, most of the dyes used in microscopy notably for biological purposes (fluorescein, rhodamine, boron-dipyrromethene dyes, and cyanines) display a small Stokes shift (Δ_{St}), that is, a small difference between the maximum of the lowest-energy absorption band and the maximum of the emission band. Indeed, in the case of the dyes listed above, Δ_{St} often lies in the 10–50 nm range. This results in the overlap of both excitation and emission bands leading to many disadvantages such as self-quenching and reabsorption effects, as well as measurement error due to excitation light and scattered light.[1,2] This can be partially corrected by the use of filters, which in turn may significantly decrease the collected emission especially in the case of a very small Stokes shifts and thus reduce the detection sensitivity to a great extent. In addition, the overlapping bands are incompatible with applications for materials such as solid-state fluorescence[3] or organic scintillators development[4,5] which require fluorophores having well-separated absorption and emission bands. To circumvent this issue, strategies based on sophisticated systems containing up to four dyes have been devised.[6,7] Owing to three consecutive transfers of excitation energy (FRET), excitation of the first fluorophore leads to the emission of the fourth, resulting in an apparent Stokes shift of 240 nm. However, an intense research effort has been focused on increasing Δ_{St} of common families of dyes.[1,8]

Consequently, there is an urgent need for simpler molecular fluorophores displaying high Δ_{St} while maintaining appreciable quantum yield. In regard to the wide range of possible applications for such dyes, their synthesis should be straightforward and versatile. For example, fluorescence properties of a common fluorogenic scaffold could be easily tuned by the incorporation of peripheral groups that modulate the electronic features of the ground and excited states.

In our ongoing research on fluorescent triphenylamine (TPA) derivatives,[9,10] we were pleased to find that the TPA fluorescence properties could be dramatically modified by switching from the extensively studied 4,4′,4″-substitution pattern toward the previously unknown 3,3′,3″-substituted derivatives (Scheme 1).

It is generally accepted that electron-donor and electron-acceptor groups linked to a benzene ring in a *meta* fashion are not conjugated. This is true in ground state. However, the work of Zimmermann et al.[11,12] and Yates and Sinha[13] demonstrated that electron delocalization occurred in the excited state.

As an example, fluorescence properties of the well-known Green Fluorescence protein (GFP) have been elegantly tuned by turning its natural *para* substitution pattern into the unusual *meta*.[14] The so-called 'meta effect' has been further investigated by Lewis[15,16] and others[17,18] on various stilbene derivatives substituted on position 3 by a donor or acceptor group. They demonstrated that the *meta*[19] isomer of a TPA/stilbene hybrid, namely (*N*,*N*-diphenylamino)stilbene, exhibits higher Δ_{St} than the *para*[20] (107 nm vs 33 nm in hexane). This prompted us to further investigate the fluorescence properties of the little studied 3,3′,3″-tris-

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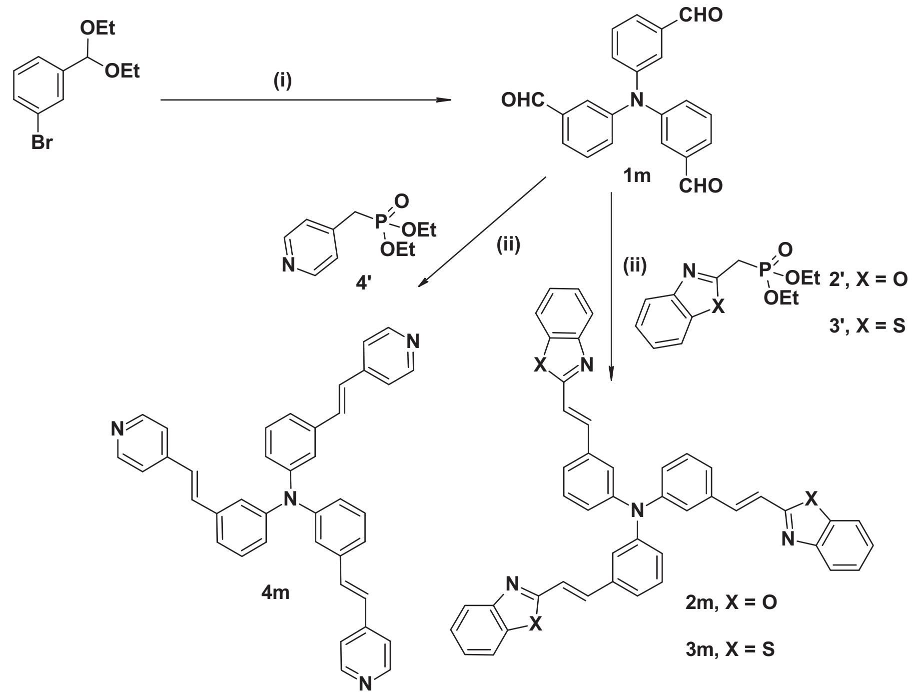
doi:10.1016/j.tetlet.2010.06.082

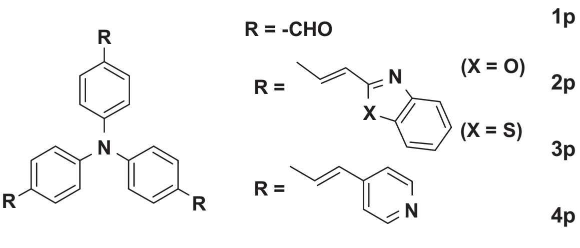


Scheme 1. Reagents and conditions: (i) $Pd_2(dba)_3$, $P(C_{12}H_9)(t\text{-}Bu)_2$, $LiNH_2$, t-BuONa, dioxane, 85 °C, 30 h, 64%; (ii) phosphonate, NaH, THF, rt, 48 h, 58–64%.

substituted-TPA (*m*-TPA). The synthesis of the m-TPAs relies on the key intermediate 3,3′,3″-tris-formyl-TPA (**1m**) which is easily obtained in one step by a Buchwald reaction between the ammonia equivalent $LiNH_2$ and an aryl bromide followed by in situ deprotection (Scheme 1).[21,22] It should be noted that the *para* counterpart **1p** (Scheme 2), could also be synthesized in only one step which compares favorably with the previously described two-step synthesis.[23,24] Starting from **1m**, the use of the Wittig reaction allows incorporation of various groups and hence the tuning of fluorescence properties.[25] In this way, compounds **2m**–**4m** were obtained with a pure *E*,*E*,*E* stereochemistry and their photophysical properties compared to that of the *para* analogs **2p**–**4p** previously synthesized (Scheme2).[10]

Considering the **m** and **p** series, several observations can be drawn (Fig. 1). Firstly the emission spectra of both the series are identical in shape and reach their maxima at a similar wavelength. Quantum yields (Φ_F) of the **m** series are around ten times lower as compared to those of their **p** counterparts (Table 1) but nonetheless stay in the range of the quantum yields of the widely used stains Cy3[26] or thiazole orange[27] (values near 0.05).

This fluorescence decrease due to *para*- versus *meta*-substituent modification has been already observed in certain cases.[18,20] In particular, in the case of structurally related *N*-diphenyl *trans*-aminostilbenes, the fluorescence quantum yields have been shown to strongly depend on the electron delocalization between the branches (involving the lone pair of the central nitrogen) and on the rate of the *trans*–*cis* photoisomerization in the excited state that causes non-radiative decay.[20]



Scheme 2.

It might well be that these two features are modified for the present vinyl TPA series while shifting from *para* to *meta* substitution. On the contrary, the absorption spectra maxima of the **m** series are strongly blue-shifted by about 100 nm as compared to those of their **p** counterparts and as expected from the lower degree of electron delocalization within the *meta* connected branches in the ground state. Finally, both **m** and **p** compounds exhibit unstructured absorption spectra and very high molar extinction coefficients that are significantly larger for compounds **2m** and **4m** (up to 100,000 M^{-1} cm^{-1}) as compared to their **2p** and **4p** isomers.

Interestingly, while absorption and emission spectra of the **p** series overlap to some extent, those of the **m** series are totally resolved

Table 1
Spectroscopic properties of *m*-TPA (**2m**–**4m**) and *p*-TPA (**2p**–**4p**)[a]

	Absorbance[b]		Emission[c]		Δ_{St} (nm)[d]
	λ (nm)	ε (M^{-1} cm^{-1})	λ (nm)	Φ_F	
2m	311	108,270	499	0.05	188
2p	424	88,980	518	0.50	94
3m	331	96,610	527	0.04	196
3p	432	97,260	534	0.52	102
4m	325	91,570	509	0.06	184
4p	406	59,450	511	0.51	105
3m[e]	332		568		236
3m[f]	327		572		245

[a] Recorded in chloroform at rt.
[b] At 10 μM.
[c] At 1 μM.
[d] Stokes shift.
[e] In EtOH.
[f] In MeCN. Quantum yields were measured using quinine bisulfate in 1 N H_2SO_4 as a reference.

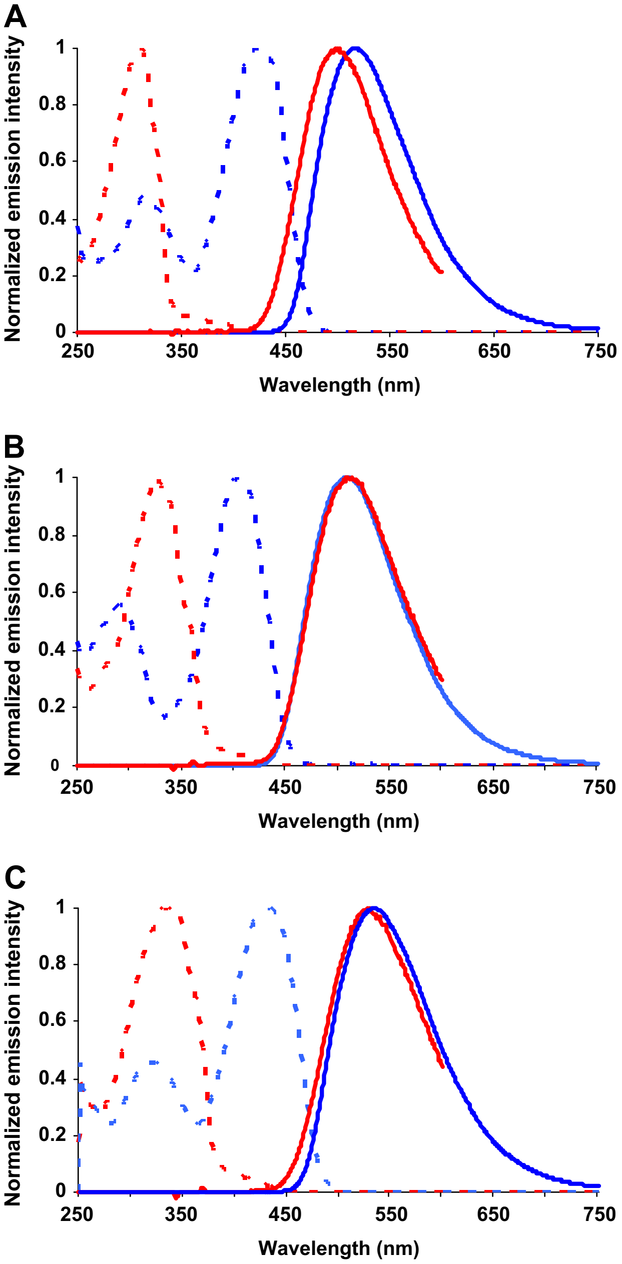


Figure 1. Normalized absorption spectra (dashed lines, recorded at 10 μM dye concentration) and fluorescence spectra (plain lines, recorded at 1 μM dye concentration) of *m*-TPA (in red) and their *para* counterparts (in blue) recorded in dichloromethane at room temperature. Compounds **2m**, **2p** (A); **3m**, **3p** (B); and **4m**, **4p** (C).

due to their impressive Δ_{St}. This phenomenon should reduce the reabsorption effect to almost zero, thereby enabling the use of these dyes in the aforementioned applications. Δ_{St} was further evaluated by solvatochromism studies performed on **3m** (Fig. 2, Table 1).

While absorption maxima are virtually independent from the solvent used, emission maxima are red-shifted with increasing polarity of the solvent, thus providing evidence for a strong internal charge transfer in the lowest singlet excited state.[19,20] In particular, a Δ_{St} value of 245 nm was obtained with **3m** in acetonitrile; this impressively high Δ_{St} largely exceeds that of most other dyes designed to exhibit high Δ_{St}.[1,4,5,28–30]

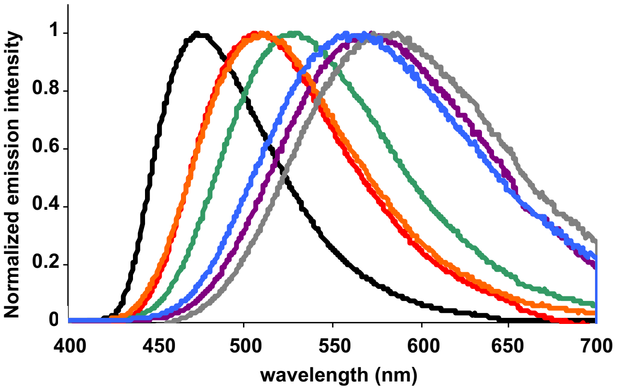


Figure 2. Normalized emission spectra of **2m** (1 μM) recorded in various solvents (from left to right: toluene, chloroform, ethyl acetate, dichloromethane, ethanol, acetonitrile, DMSO) at rt.

In conclusion, the novel 3,3′,3″-trisformyl compound **1m** is found to be a versatile and easy-to-synthesize precursor enabling the preparation of fluorescent vinyl derivatives displaying exceptionally large Δ_{St}. This is illustrated herein by the three compounds (**2m**, **3m**, and **4m**) which feature the *m*-TPA scaffold thus displaying base-to-base resolved absorption and emission spectra. Consequently, the new family of *m*-TPA represents a robust starting point for the development and fluorescence engineering of dyes circumventing reabsorption problems.

Acknowledgment

The authors wish to thank Dr. Jason Martin for careful reading of the manuscript.

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22. *Synthesis of* **1m**: In dry and degassed dioxane (4 mL) were suspended Pd$_2$(dba)$_3$ (121 mg, 132 μmol, 3%) and P(*o*-C$_6$H$_4$–C$_6$H$_5$)(*t*-Bu)$_2$ (100 mg, 335 μmol, 7.5%). After 15 min of stirring were added 3-bromobenzaldehyde diethylacetal (2.85 mL, 13.98 mmol, 3.2 equiv), lithium amide (100 mg, 4.35 mmol, 1 equiv), and *t*-BuONa (1.25 g, 13.06 mmol, 3 equiv). The resulting suspension was heated at 85 °C for 30 h. Then Pd$_2$(dba)$_3$ (121 mg) and P(*o*-C$_6$H$_4$–C$_6$H$_5$)(*t*-Bu)$_2$ (100 mg) were added and the mixture was heated for 16 additional hours. The mixture was cooled down to room temperature, diluted

by CH_2Cl_2, and washed with HCl 1 M and water. Organic layer was dried over $MgSO_4$ and concentrated. The resulting yellow oil was purified by column chromatography (*n*-hexane/CH_2Cl_2, 1:1–1:0, v/v). Trituration in Et_2O afforded 363 mg (1.10 mmol) of the title compound in 25% yield. mp 149–150 °C. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.39 (m, 3H), 7.51 (t, *J* = 7.8 Hz, 3H), 7.61 (m, 3H), 7.63 (m, 3H), 9.96 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 191.5, 147.7, 138.1, 130.6, 130.0, 125.7, 124.2. HRMS (DCI+) calcd for $C_{21}H_{16}NO_3$, 330.1130; found 330.1127.

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25. *A typical procedure for Wittig reaction*: In dry THF (15 mL) were added diethyl-[(benzothiazol-2-yl)methyl)]phosphonate (288 mg, 1.00 mmol, 3.3 equiv) and NaH (27 mg, 1.12 mmol, 3.7 equiv, 60% in mineral oil). After 15 min of stirring, a solution of **1m** (100 mg, 304 μmol, 1 equiv) in THF (5 mL) was added and the resulting mixture was stirred at room temperature for 48 h in the dark. Water and dichloromethane were added, and after decantation the aqueous layer was extracted 3 times with dichloromethane and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude residue was purified by dissolution in a minimal amount of dichloromethane, precipitated with pentane, and filtered to afford **3m** as a yellow powder (195 μmol, 140 mg) in 64% yield. Mp 118 °C (dec). ^{1}H NMR (300 MHz, acetone d6) *δ*: 7.19 (m, 3H), 7.37–7.56 (m, 18H), 7.63 (d, *J* = 16.2 Hz, 3H), 7.94 (d, *J* = 8.6 Hz, 3H), 7.99 (d, *J* = 8.6 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) *δ*: 166.8, 153.9, 148.1, 137.2, 137.0, 134.4, 130.1, 126.3, 125.4, 125.3, 123.2, 123.0, 122.7, 122.3, 121.5. HRMS (DCI+) calcd for $C_{45}H_{31}N_4S_3$, 723.1711; found 723.1721. Compounds **2m** and **4m** were obtained using the same procedure and the corresponding phosphonate: **4m** pale yellow powder. Mp 132–134 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 6.93 (d, *J* = 16.3 Hz, 3H), 7.10 (d, *J* = 7.6 Hz, 3H), 7.18–7.32 (m, 18H), 8.55 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 120.77, 121.56, 122.85, 124.57, 126.36, 129.88, 132.69, 137.54, 144.32, 147.96, 150.04. MS (ESI+) *m*/*z* 555.2 $[M+H]^+$ (100%), 577.3 $[M+Na]^+$ (10%). **2m**, pale yellow powder. Mp 136–138 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 7.00 (d, *J* = 16.3 Hz, 3H), 7.18 (d, *J* = 6.5 Hz, 3H), 7.26–7.35 (m, 15H), 7.48–7.50 (m, 3H), 7.68–7.73 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 110.27, 114.42, 119.85, 122.29, 123.26, 124.47, 125.23, 125.45, 130.10, 136.65, 138.91, 142.08, 147.87, 150.34, 162.56. MS (ESI+): *m*/*z* 675.3 $[M+H]^+$ (100%), 697.2 $[M+Na]^+$ (70%).
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