HOW TO READ A SCIENTIFIC PAPER

Rebecca Strada

WHAT IS A SCIENTIFIC PAPER?

- Scientific papers (also known as 'journal articles') are a particular type of written work with a few characteristics:
  - published in a periodical called a journal, whose purpose is to publish this kind of work
  - peer-reviewed
  - citable
  - include citations

- Scientific papers are for sharing your own research work or reviewing the research conducted by others
- Scientific papers have two audiences: the referees and the journal readers

TYPES OF SCIENTIFIC PAPERS

- Based on original research
- Experiments/analysis
- Data interpretation

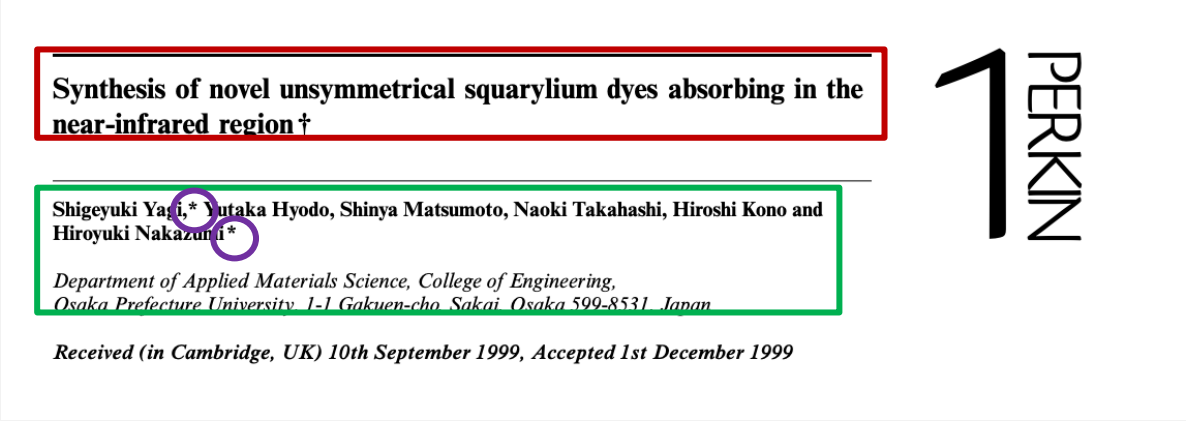
THE STRUCTURE OF A SCIENTIFIC PAPER

The general outline is the following:

- ❑ Title
- ❑ Author(s)
- ❑ Abstract
- ❑ Introduction
- ❑ Materials & Methods
- ❑ Results
- ❑ Discussion
- ❑ References/Literature Cited

TITLE

- Title
- Authors and affiliations
- Corresponding author(s) + contact information
- Keywords



Synthesis of novel unsymmetrical squarylium dyes absorbing in the near-infrared region †

Shigeyuki Yagi,* Yutaka Hyodo, Shinya Matsumoto, Naoki Takahashi, Hiroshi Kono and Hiroyuki Nakazumi*

Department of Applied Materials Science, College of Engineering, Osaka Prefecture University, 1-1 Gakuen-cho, Sakai, Osaka 599-8531, Japan

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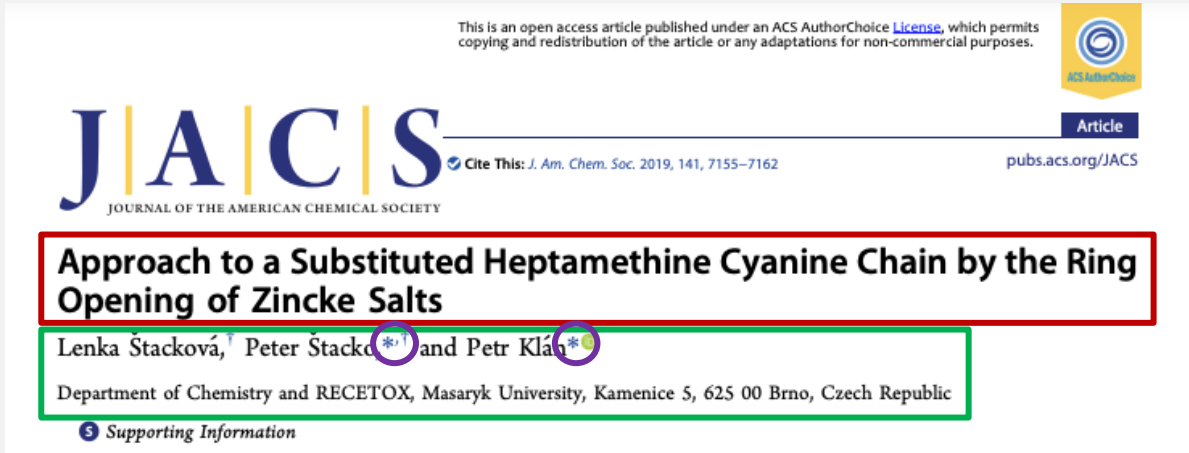

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Approach to a Substituted Heptamethine Cyanine Chain by the Ring Opening of Zincke Salts

Lenka Štacková,† Peter Stacko,‡ and Petr Klán*,†

Department of Chemistry and RECETOX, Masaryk University, Kamenice 5, 625 00 Brno, Czech Republic

Supporting Information

ABSTRACT

- highlight key points from major sections of the paper
- explain what is included in the paper
- Typical length is 200-250 words

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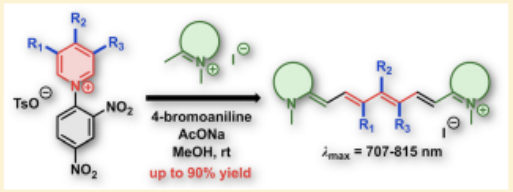
Lenka Štacková,† Peter Štacko,*,† and Petr Klán*

Department of Chemistry and RECETOX, Masaryk University, Kamenice 5, 625 00 Brno, Czech Republic

Supporting Information

ABSTRACT: Cyanine dyes play an indispensable and central role in modern fluorescence-based biological techniques. Despite their importance and widespread use, the current synthesis methods of heptamethine chain modification are restricted to coupling reactions and nucleophilic substitution at the meso position in the chain. Herein, we report the direct transformation of Zincke salts to cyanine dyes under mild conditions, accompanied by the incorporation of a substituted pyridine residue into the heptamethine scaffold. This work represents the first general approach that allows the introduction of diverse substituents and different substitution patterns at the C3′−C5′ positions of the chain. High yields, functional tolerance, versatility toward the condensation partners, and scalability make this method a powerful tool for accessing a new generation of cyanine derivatives.



Synthesis of novel unsymmetrical squarylium dyes absorbing in the near-infrared region †

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Department of Applied Materials Science, College of Engineering, Osaka Prefecture University, 1-1 Gakuen-cho, Sakai, Osaka 599-8531, Japan

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Novel unsymmetrical squarylium dyes which absorb in the near-infrared region were synthesized by a stepwise procedure *via* intermediate 4-substituted 3-hydroxycyclobut-3-ene-1,2-diones. By introducing benz[*c*,*d*]indoline or benzo[*b*]pyran moieties at one end as an electron-donating component, the SQ dyes exhibited their absorption maxima at 739–821 nm with large molar absorption coefficients (log ε = 4.96–5.18) in $CHCl_3$. The X-ray analysis for one of these dyes was also examined to confirm the overall structure of the unsymmetrical SQ dye.

INTRODUCTION

Since their first synthesis in 1856, cyanine dyes have become invaluable fluorophores in contemporary chemistry and biology.[1] The defining feature of the cyanines is an odd-numbered polyene linking two nitrogen-containing heterocycles, related to both their intriguing photophysical properties and unique chemical reactivities.[2] Within this family, heptamethine cyanines dyes (Cy7, Figure 1a), containing seven carbon atoms in the linker, are particularly valued for their absorption and emission maxima located in the center of the near-infrared (NIR) window (~800 nm).[3] In biology, the presence of endogenous chromophores, such as hemoglobin and water, and optical scattering limit the depth of light penetration into tissues. Light absorption in the phototherapeutic window (600−1000 nm), where these effects are minimized, thus ensures a broad scope of biological applications.

The expanding medical significance of Cy7 dyes is demonstrated by FDA-approved indocyanine green (ICG) with hundreds of clinical trials emerging even after 50 years of its clinical use (Figure 1b).[4] Another promising derivative, IR800-CW, has been explored for a number of fluorescence-guided surgery applications (Figure 1b).[5−7] Furthermore, cyanines have been used in a number of other applications, including pH sensing,[8,9] analyte-responsive sensing,[2,10] glutathione[11] or reactive oxygen species[12−14] visualization, single-molecule fluorescence and super-resolution imaging,[15−17] photodynamic therapy,[18,19] NIR photouncaging,[20,21] and others.[22] These applications take advantage not only of their excellent photophysical properties but also the distinct chemical reactivity of the cyanine polyene itself.[23]

The nature of heptamethine chain substituents has a profound influence on both the photophysical and photochemical properties of the Cy7 dyes as well as their chemical stability.

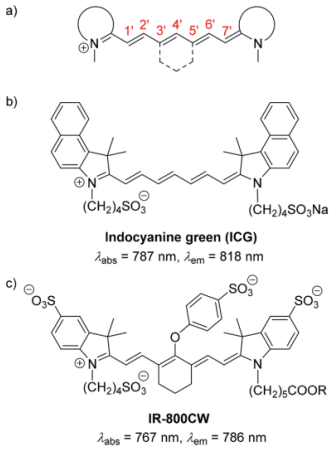

Figure 1. (a) Heptamethine cyanine dyes (Cy7). The numbering of the heptamethine chain is depicted in red. (b) Indocyanine green. (c) IR-800CW.

The introduction of electron-withdrawing nitrile,[24] amide,[25] or triazole[26] moieties in the chain meso position improves the dye photostability as a result of decreased reactivity toward singlet oxygen. The installation of the 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO)-bearing substituent at the C4′ position resulted

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in an ~33-fold increase in the quantum yield of singlet oxygen formation compared to that of ICG sensitization.[27] Bioconjugation of cyanines commonly achieved via the attachment of C4′-*O*-aryl or C4′-*S*-alkyl linkers often suffers from poor chemical stability of the conjugate toward biologically relevant nucleophiles, such as glutathione or cellular proteins.[28−30] One way to circumvent this issue is to employ C4′-*O*-alkyl-substituted cyanines which have so far been accessible only by Smiles rearrangement of C4′-*N*-methylethanolamine precursors.[31] In addition, an elegant design of the C4′-dialkylamine linker bearing a carbamate functionality allowed us to harness the undesired photooxidiation in a NIR photouncaging process.[20,21]

Despite the widespread utilization of cyanines and the evident importance of polyene substitution, the strategies used to modify the heptamethine chain remain surprisingly underdeveloped and limited. A majority of the current methods start from the C4′-chloro-substituted cyanine and rely on an electron-transfer-mediated $S_{RN}1$ reaction with N, O, or S nucleophiles[13,25,32−38] or palladium-catalyzed Suzuki[39] or Sonogashira[40] coupling reactions (Scheme 1a). The other option involves the preparation of a custom Schiff base intermediate from a substituted cyclohexene in the Vilsmeier−Haack reaction (Scheme 1b). However, this procedure gives moderate yields only for methyl- and phenyl-substituted cyclohexenes presumably because of harsh conditions employed in the synthesis.[41,42] Besides a cyclopentyl or cyclohexyl ring embedded within the heptamethine scaffold, no modifications at the C3′ and C5′ positions have been reported to date. Therefore, essentially only the C4′-position modifications are available for modification to date, imposing fundamental restrictions on the design of new Cy7 fluorophores. Herein, we report the first general synthesis method to access Cy7 dyes possessing diverse substituents and substitution patterns at the C3′−C5′ positions of a heptamethine chain under mild conditions (Scheme 1c).

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INTRODUCTION

- ❑ Describe **the nature of the problem**
- ❑ Distillation of **the relevant literature**
- ❑ Development of **the rationale of the study**

What can you find in this section?

- ❑ First paragraph: what is known about the topic? What is the current/latest knowledge?
- ❑ Second paragraph: what are the problems/gaps in existing knowledge/unanswered questions? What are the limitations of the existing solutions?
- ❑ Third paragraph: What questions are you trying to answer? What problems are you trying to solve?

MATERIALS & METHODS

- describes how the experiments have been conducted
  - instruments information
  - instrument set up
  - method/procedure used for a particular experiment
  - additional data
- allow the reader **to repeat the experiments**
- allow the reader **to evaluate the results**
- the method can be new (described in full) or established (a reference will be found here to some older paper)

results obtained here should stimulate development of synthesis of SQ dyes, aiming at application to optics devices.

Experimental

^{1}H NMR spectra (270 MHz) were recorded on a JEOL JNM-GX 270 spectrometer in $CDCl_3$ and DMSO-d_6 using TMS (0 ppm) and CHD_2SOCD_3 (2.49 ppm) as internal standards, respectively. IR spectra were taken for KBr disks of samples and recorded on a HORIBA FT-200 spectrometer. Mass spectra were obtained by EI and FAB techniques on a Finnigan MAT MS spectrometer. For the FAB-mass spectroscopic measurement, 3-nitrobenzyl alcohol was used as a matrix. Melting points were determined by differential thermal analyses with a RIGAKU TAS 100 analyzer under nitrogen atmosphere (flow rate: 100 mL min^{-1}) using Al_2O_3 as a reference. The temperature-raising rate programmed was 10 °C min^{-1}.

Benzindolium **8** was obtained by the reported procedure.[10] ^{1}H NMR data and elemental analyses for **8a** and **8b** are available as supplementary materials. Benzopyrylium **9** was prepared according to the reported procedure.[11] Dyes **16**[12] and **17**[5d] were obtained by the usual procedure[4] from julolidine (2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline) and benzindolium **8c**, respectively.

4-(*N*,*N*-Dibutylaminophenyl)-3-chlorocyclobut-3-ene-1,2-dione 4a

A mixture of **1a** (2.05 g, 9.98 mmol) and **3** (2.26 g, 15.0 mmol) in CH_2Cl_2 (20 mL) was stirred for 24 h at ambient temperature. The solvent was removed by a rotary evaporator, and the residue was purified by silica gel column chromatography (benzene as eluent) to afford **4a** as a yellow solid; yield, 22%; mp 80 °C; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J = 7.3 Hz, 6H), 1.39 (sextet, J = 7.3 Hz, 4H), 1.63 (quintet, J = 7.3 Hz, 4H), 3.40 (t, J = 7.3 Hz, 4H), 6.76 (d, J = 9.2 Hz, 2H), 8.13 (d, J = 9.2 Hz, 2H); IR (KBr) 1795, 1759 cm^{-1} (C=O); EI-MS *m*/*z* 319 (M^+, 100%), 321 (M^+ + 2, 26%); Anal. Calcd for $C_{18}H_{22}NO_2Cl$: C, 67.60; H, 6.93; N, 4.38%. Found: C, 67.79; H, 7.00; N, 4.45%.

4-(2,3,6,7-Tetrahydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinolin-9-yl)-3-chlorocyclobut-3-ene-1,2-dione 4b

A mixture of **1b** (1.73 g, 9.98 mmol) and **3** (1.81 g, 12.0 mmol) in CH_2Cl_2 (20 mL) was stirred for 24 h at ambient temperature. The solvent was removed by a rotary evaporator, and the residue was purified by silica gel column chromatography (CH_2Cl_2 as eluent) followed by recrystallization from $CHCl_3$ to afford **4b** as an orange solid; yield, 39%; mp 208 °C (decomp.); ^{1}H NMR ($CDCl_3$) δ 1.98 (quintet, J = 6.1 Hz, 4H), 2.77 (t, J = 6.1 Hz, 4H), 3.37 (t, J = 6.1 Hz, 4H), 7.69 (s, 2H); IR (KBr) 1774, 1749 cm^{-1} (C=O); EI-MS *m*/*z* 231 ([M − 2CO]$^+$, 100%), 233 ([M − 2CO]$^+$ + 2, 31%), 287 (M^+, 30%), 289 (M^+ + 2, 9.7%); Anal. Calcd for $C_{16}H_{14}NO_2Cl$: C, 66.79; H, 4.90; N, 4.87%. Found: C, 66.30; H, 4.61; N, 5.22%.

([M − 2CO − CH_3]$^+$ + 2, 33%), 231 ([M − 2CO]$^+$, 70%), 233 ([M − 2CO]$^+$ + 2, 24%), 287 (M^+, 28%), 289 (M^+ + 2, 11%); Anal. Calcd for $C_{16}H_{14}NO_2Cl$: C, 66.79; H, 4.90; N, 4.87. Found: C, 66.98; H, 4.74; N, 4.96%.

4-(*N*,*N*-Dibutylaminophenyl)-3-hydroxycyclobut-3-ene-1,2-dione 6a

A solution of **4a** (704 mg, 2.2 mmol) in AcOH–water (4:1, v/v, 9 mL) was stirred at reflux for 4 h. After cooling, the precipitate was separated by filtration, and stirred in ether–hexane (1:1, v/v, 20 mL) for 30 min. Filtration afforded **6a** as a yellow solid; yield, 83%; mp 253 °C (decomp.); ^{1}H NMR (DMSO-d_6) δ 0.90 (t, J = 7.3 Hz, 6H), 1.31 (sextet, J = 7.3 Hz, 4H), 1.48 (m, 4H), 3.40 (m, 4H), 6.85 (d, J = 7.9 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H) (the OH proton was not observed); IR (KBr) 1763, 1716 cm^{-1} (C=O); FAB-MS *m*/*z* 302 ([M + H]$^+$); Anal. Calcd for $C_{18}H_{23}NO_3 \cdot 0.5H_2O$: C, 69.65; H, 7.79; N, 4.51. Found: C, 70.45; H, 7.73; N, 4.48%.

4-(2,3,6,7-Tetrahydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinolin-9-yl)-3-hydroxycyclobut-3-ene-1,2-dione 6b

A solution of **4b** (905 mg, 3.4 mmol) in AcOH–water (4:1, v/v, 30 mL) was stirred at reflux for 4 h. After cooling, the precipitate was separated by filtration, and stirred in ether (100 mL) for 30 min. Filtration afforded **6b** as a yellow solid; yield, 81%; mp 248 °C (decomp.); ^{1}H NMR (DMSO-d_6) δ 1.86 (quintet, J = 6.1 Hz, 4H), 2.69 (t, J = 6.1 Hz, 4H), 3.26 (t, J = 6.1 Hz, 4H), 7.40 (s, 2H) (the OH proton was not observed); IR (KBr) 1763, 1716 cm^{-1} (C=O); EI-MS *m*/*z* 213 ([M − 2CO]$^+$, 100%), 269 (M^+, 61%); Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.07; H, 5.43; N, 4.93%.

4-(1,3,3-Trimethylindolin-2-ylidenemethyl)-3-hydroxycyclobut-3-ene-1,2-dione 7

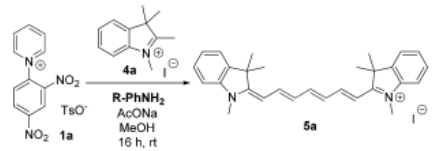
A solution of **5** (2.23 g, 7.75 mmol) in AcOH–water (4:1, v/v, 22 mL) was stirred at reflux for 5 h. After cooling, the precipitate was separated by filtration. Purification by ODS column chromatography (Nakalai Tesque, inc., Cosmosil 75C_{18}-OPN, MeOH–water (2:1, v/v) as eluent) followed by recrystallization from CH_2Cl_2 afforded **7** as a yellow solid; yield, 37%; mp 205 °C (decomp.); ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 6H), 3.34 (s, 3H), 5.45 (s, 1H), 7.01 (d, J = 7.3 Hz, 1H), 7.11 (t, J = 7.3 Hz, 1H), 7.25 (t, J = 7.3 Hz, 1H), 7.38 (t, J = 7.3 Hz, 1H) (the OH proton was not observed); IR (KBr) 1764, 1726 cm^{-1} (C=O); EI-MS *m*/*z* 198 ([M − 2CO − CH_3]$^+$, 100%), 269 (M^+, 28%); Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.43; H, 5.55; N, 5.19%.

RESULTS AND DISCUSSION

Typically, the Zincke reaction is used to convert pyridines to *N*-pyridinium salts by the reaction of *N*-2,4-dinitrophenyl-pyridinium (Zincke salt) with primary amines at elevated temperatures (Scheme 2, route A).[43] We envisioned that, under specific conditions, intermediate **2** produced by the ring opening of pyridinium salt **1**, as suggested in the synthesis of benzothiazole Cy7 derivatives with an unsubstituted heptamethine chain,[44] could instead be intercepted by another equivalent of aniline as a nucleophile, and resulting intermediate **3** would undergo a condensation with quaternized heterocycle **4** to give the final cyanine **5** in a one-pot tandem fashion (Scheme 2, route B). In such a manner, the substituents on the pyridine residue would be transferred and incorporated into the cyanine as a part of the heptamethine scaffold. We also hypothesized that the ring opening of very electron-deficient pyridinium salts could also be performed directly with **4** without the need for any auxiliary nucleophile.

We synthesized a number of pyridinium salts **1a**–**v** on a multigram scale by the reaction of 2,4-dinitrophenyl (DNP) tosylate or triflate with substituted pyridines at an elevated temperature (Supporting Information). The salts were isolated in high purity simply by filtration and proved to be benchtop-stable for months. Subjecting **1a** to a reaction with heterocycle **4a** in the presence of sodium acetate (6 equiv) and in the absence of aniline at room temperature overnight provided corresponding cyanine **5a** in 24% yield (Table 1, entry 1). The

Table 1. Optimization of the Preparation of Cyanine 5a from Zincke Salt 1a[a]



entry	R-PhNH$_2$	aniline	AcONa	yield[b]
1			6 equiv	24%
2	4-H	3 equiv	6 equiv	47%
3	4-MeO	3 equiv	6 equiv	<2%
4	4-Br	3 equiv	6 equiv	73%
5	4-CN	3 equiv	6 equiv	34%
6	4-Br	1.2 equiv	6 equiv	72%
7	3-Br	1.2 equiv	6 equiv	73%
8	3-Br	1.2 equiv	4 equiv	60%
9	4-Br	0.2 equiv	6 equiv	35%
10	4-Br	0.2 equiv	3 equiv	22%

[a]Reaction conditions: **1a** (0.5 mmol), **4a**(1.5 mmol), aniline, and sodium acetate in methanol (5 mL) were stirred at room temperature for 16 h. [b]Isolated yields are given.

addition of excess aniline (3 equiv) to facilitate ring opening of the pyridinium salt improved the yield to 47% (entry 2). Encouraged by this finding, we examined the electronic effects of the aniline substituents on the reaction yield. The use of a strong electron-donating (EDG) 4-methoxy substituent led to rapid pyridinium ring opening as evidenced by the development of a deep-red coloration of the reaction mixture (λ_{max} = 485 nm),[45] whereas the corresponding cyanine was produced only in trace amounts (entry 3). The presence of intermediate **3** was further confirmed in a reaction of **1a** and aniline using HPLC and UV–vis spectroscopy by comparison with an authentic sample of **3** (Figures S154 and S155). Conversely, the use of a strong electron-withdrawing (EWG) 4-cyano substituent led to only a marginal increase in the yield compared to that of an unanalyzed reaction (34%, entry 5). On the contrary, weakly electron accepting 4- or 3-bromo substituents dramatically improved the yield to 72 and 73%, respectively (entries 4 and 7). Decreasing the aniline amount to 1 equiv had no negative effect on the yield, whereas its further decrease to substoichiometric amounts or reducing the number of equivalents of sodium acetate led to lower yields of **5a** (entries 6–10). *N*-Phenylpyridinium was observed as a major side product upon the temperature increase as a result of intramolecular Schiff base cyclization.[43]

The dependence of cyanine formation yields on the nature of aniline substituents implies a delicate interplay of electronic effects. An aniline reagent is required to be electron-rich enough to facilitate pyridinium ring opening and, at the same time, be sufficiently electron-poor to activate the resulting imine for a facile condensation with the heterocycle. Thus, while 4-methoxyaniline expedites a rapid cleavage of the pyridinium ring, corresponding electron-rich imine **3** reacts too slowly in the subsequent condensation (and vice versa for 4-cyanoaniline). Established empirically, 3- and 4-bromoaniline facilitated both steps with a desirable efficiency and thus the highest yields.

Following the optimization, we sought to investigate the scope of this method and its tolerance toward various substituents and substitution patterns. A variety of substituted pyridinium salts **1a**–**t** were examined in the reaction with **4a**, and the results are summarized in Table 2. In most cases, the pure products were isolated directly by filtration of the precipitate from the reaction mixture. The products were, in some cases, contaminated with 2,4-dinitroaniline, which was removed by rapid column chromatography.

The method is versatile, and it tolerates both electron-withdrawing and electron-donating groups on the pyridinium ring. The pyridinium salts with EWGs reacted faster and usually with higher yields (vide infra) than those with EDGs. A decreased reactivity of pyridines with mediocre EDGs (**1b**, **1m**) under the optimized conditions was compensated for by a higher loading of 4-bromoaniline (3 equiv). On the other hand, **1n** did not undergo the ring-opening reaction under these conditions, presumably because of a strong resonance electron-donating effect of the methoxy substituent. We reasoned that employing a less polar solvent, such as ethanol or pyridine, would lead to less favorable solvation of the pyridinium salt, thus promoting the pyridinium ring opening. Indeed, when the reaction was carried out in pyridine, cyanine **5n** was successfully isolated in 40% yield. On the contrary, strong EWGs (**1d**, **1g**, and **1k**) did not actually demand the presence of aniline as an auxiliary nucleophile, and the pyridinium ring opening could be achieved efficiently in its absence. Our observations are consistent with the mechanism of the Zincke reaction and the subsequent condensation, both of which involve a nucleophilic attack and therefore require a sufficiently electron-deficient substrate (Scheme 2).

Both C3′-alkyl- and C3′-aryl-substituted pyridinium salts gave cyanines **5b** and **5c** in very good yields. Substrates bearing halogens also efficiently afforded products **5d**–**5f** in yields of 49–90%, increasing in the order of increasing halogen electronegativity. Various functional derivatives of carboxylic acids, such as esters (**5g** and **5h**), carboxylic acid (**5i**), amide (**5j**), and nitrile (**5k**), as well as an acyl derivative (**5l**) were well

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RESULT & DISCUSSION

- usually combined because results make little sense to most readers without the discussion
- usually contains tables, graphs, and figures
- describe and interpret what has been observed
- relate to previous observations

CONCLUSIONS

CONCLUSIONS

The utilization of the Zincke salts ring opening in the cyanine synthesis reported herein represents the first general method for the derivatization of the heptamethine chain. Using this approach, the substituted pyridine backbone is transferred and incorporated into a cyanine dye as a part of the heptamethine chain. A wide variety of substituents can thus be installed at different positions of the chain, and different heterocycles can be employed as condensation partners under mild conditions and in high yields and purities. This method constitutes a very powerful addition to the limited arsenal of tools available for the synthesis of substituted cyanines and promises the emergence of more complex cyanine-based molecules tailored for specific applications.

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REFERENCES

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SUPPORTING INFORMATION

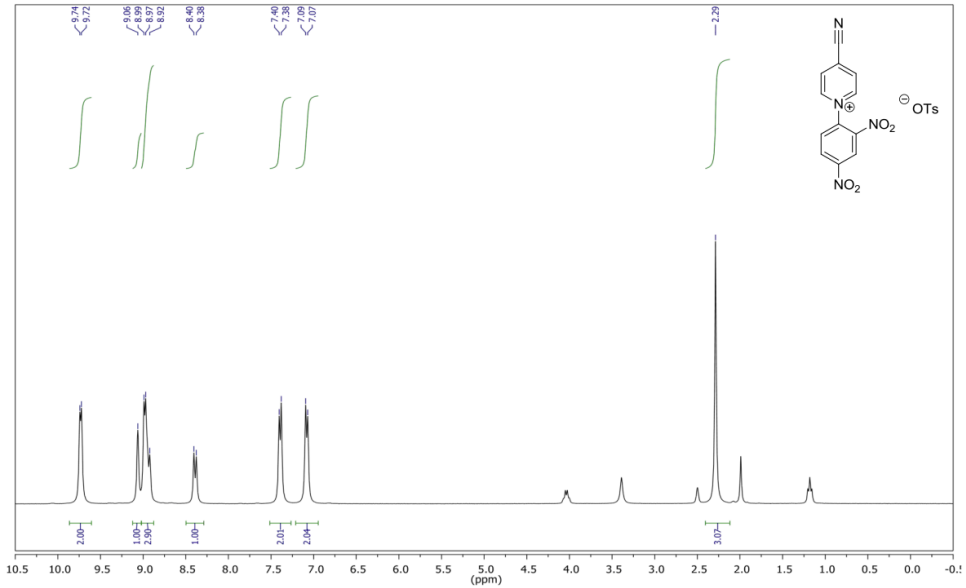
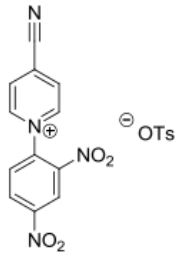
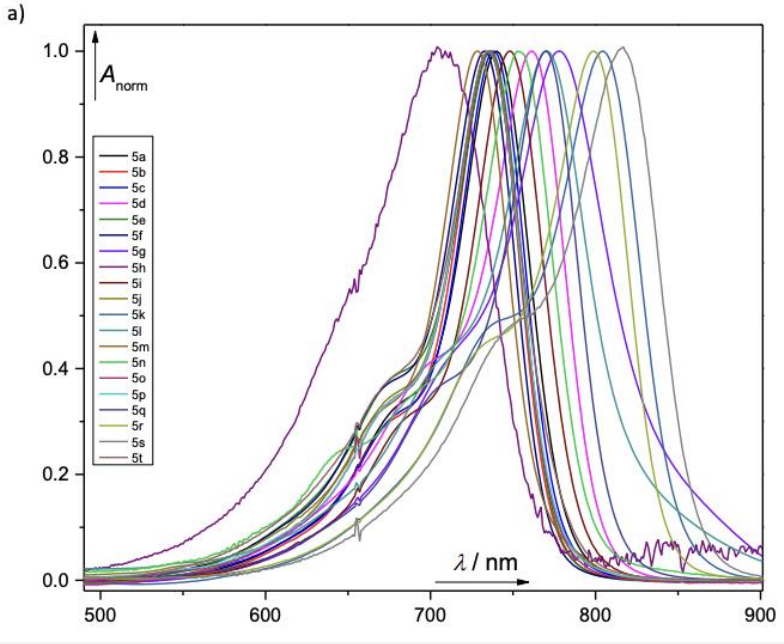


Figure S33. ^{1}H NMR (300 MHz, d_6–DMSO): **1k**

4-Cyano-1-(2,4-dinitrophenyl)pyridin-1-ium *p*-Toluenesulfonate (1k).



Prepared according to the general procedure from 4-pyridinecarbonitrile (1.80 g, 17.3 mmol) and **13** (1.95 g, 5.76 mmol) by heating the mixture neat at 110 °C. Yield: 2.31 g (91%). Yellowish solid. Mp. 205–208 °C. ^{1}H NMR (300 MHz, d_6–DMSO): δ (ppm) 9.73 (d, J = 5.5 Hz, 2H), 9.06 (s, 1H), 9.02–8.88 (m, 3H), 8.39 (d, J = 8.6 Hz, 1H), 7.39 (d, J = 7.5 Hz, 2H), 7.08 (d, J = 7.4 Hz, 2H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, d_6–DMSO): δ (ppm) 149.2, 147.8, 145.4, 142.6, 138.3, 137.7, 131.7, 130.8, 130.2, 129.7, 128.0, 125.4, 121.3, 114.6, 20.7. HRMS (ESI+): calcd. for $C_{19}H_{13}N_4O_4^+$ [M – TsO$^-$] 271.0462, found



PAPERS

The general outline is the following:

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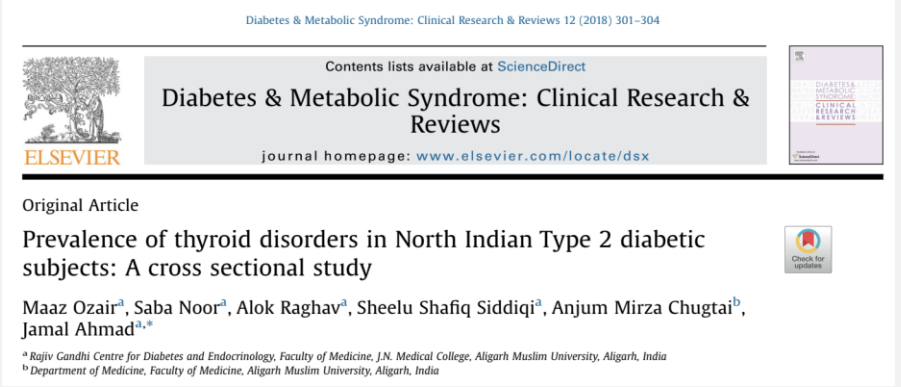

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Original Article

Prevalence of thyroid disorders in North Indian Type 2 diabetic subjects: A cross sectional study

Maaz Ozair[a], Saba Noor[a], Alok Raghav[a], Sheelu Shafiq Siddiqi[a], Anjum Mirza Chugtai[b], Jamal Ahmad[a,*]

[a] Rajiv Gandhi Centre for Diabetes and Endocrinology, Faculty of Medicine, J.N. Medical College, Aligarh Muslim University, Aligarh, India
[b] Department of Medicine, Faculty of Medicine, Aligarh Muslim University, Aligarh, India

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Open Access Article

Metals and Trace Elements in Calcified Valves in Patients with Acquired Severe Aortic Valve Stenosis: Is There a Connection with the Degeneration Process?

by Aleš Tomášek [1], Jan Mañoušek [2], Jan Kuta [3], Jiří Hlásenský [2,*], Leoš Křen [4], Martin Šindler [5], Michal Zelený [5], Petr Kala [2] and Petr Němec [1]

[1] Centre for Cardiovascular Surgery and Transplantation, Pekařská 53, 656 91 Brno, Czech Republic
[2] Department of Internal Cardiology Medicine, University Hospital and Faculty of Medicine, Masaryk University, Jihlavská 20, 625 00 Brno, Czech Republic
[3] Research Centre for Toxic Compounds in the Environment (RECETOX), Faculty of Science, Masaryk University, Kamenice 5, 625 00 Brno, Czech Republic
[4] Institute of Pathology, University Hospital and Faculty of Medicine, Masaryk University, Jihlavská 20, 625 00 Brno, Czech Republic
[5] Institute of Forensic Medicine, St Anne's University Hospital and Faculty of Medicine, Masaryk University, Tvrdého 2a, 662 99 Brno, Czech Republic
* Author to whom correspondence should be addressed.

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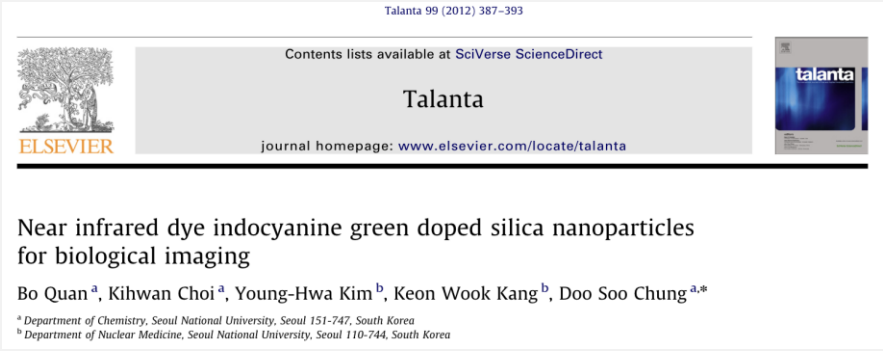

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Near infrared dye indocyanine green doped silica nanoparticles for biological imaging

Bo Quan [a], Kihwan Choi [a], Young-Hwa Kim [b], Keon Wook Kang [b], Doo Soo Chung [a,*]

[a] Department of Chemistry, Seoul National University, Seoul 151-747, South Korea
[b] Department of Nuclear Medicine, Seoul National University, Seoul 110-744, South Korea

- rebecca.strada@recetox.muni.cz