ChemComm

COMMUNICATION

Check for updates

Cite this: Chem. Commun., 2018, 54, 12463

Received 7th August 2018, Accepted 11th October 2018

DOI: 10.1039/c8cc06444j

rsc.li/chemcomm

Synthesis of symmetrical and unsymmetrical triarylpyrylium ions *via* an inverse electron demand Diels-Alder reaction[†]

C. T. Fathimath Salfeena,^{ab} Basavaraja,^{ab} K. T. Ashitha,^{ab} V. Praveen Kumar,^{ab} Sunil Varughese,^{ab} Cherumuttathu H. Suresh^b ab and B. S. Sasidhar^b *^{ab}

Dilthey et al. 1916

Bos et al. 1963

R

Our work

 $BF_3 \cdot OEt_2$ mediated inverse electron demand Diels-Alder (IEDDA) reaction of chalcones with aryl acetylenes is reported for the synthesis of symmetrical and unsymmetrical 2,4,6-triarylpyrylium ions. The protocol provides an effective one-pot method for the utilization of readily available simple substrates under mild reaction conditions leading to a diverse array of pyrylium ions in moderately good yield.

Triarylpyrylium salts feature prominently in the repertoire of synthetic molecules due to their wide range of applications in synthetic, medicinal and material chemistry.¹ Aromaticity of pyrylium salts makes them susceptible to nucleophilic reactions and are remarkable precursors for the synthesis of pyridinium, pyridine, phosphinine, thiopyrylium cores, *etc.*² Because of tunable fluorescence properties, substituted pyrylium ions have been used as photosensitizers,^{1b,3} Q-switchers,^{4,5} laser dyes,⁶ organic luminophores⁷ and in solar cells.⁸

The diversified industrial applications of pyrylium salts led to the exploration of various methods for their synthesis in the early 20th century. Among them, the most established methodology is the cyclization of 1,5-dione (Scheme 1a).⁹ In 1935, Dovey and Robinson reported a two component synthesis of triarylpyrylium using acetophenone and dypnone with very low yield.¹⁰ In 1963, Bos and Arens reported the pyrylium cations as a byproduct in the addition reaction of carbonyl compounds to alkynes (Scheme 1b).¹¹ Further, metal catalyzed rearrangement of triarylcyclopentadienes was reported in 2003.¹² The main

^a Chemical Sciences and Technology Division, CSIR-National Institute for

 $\begin{array}{c} \overrightarrow{\textbf{R}} + \overrightarrow{\textbf{R}} & + \overrightarrow{\textbf{R}} & = \overrightarrow{\textbf{R}}_{3}.OEt_{2} \\ \overrightarrow{\textbf{Cyclohexane}} & \overrightarrow{\textbf{R}} & \overrightarrow{\textbf{R}}_{9} & \overrightarrow{\textbf{R}}_{9} \\ \overrightarrow{\textbf{R}}_{1}, \overrightarrow{\textbf{R}}_{2} = Aryl, \text{ heteroaryl} \\ \overrightarrow{\textbf{Symmetrical and unsymmetrical pyrylium ions}} \\ \hline{\textbf{Scheme 1}} & \emph{Strategies employed for the synthesis of pyrylium ions.} \\ \end{array}$

BF3.OEt2

BF₃.OEt₂

R₁=Arv

limitations of the existing methods are low yields, tedious separation process and only symmetrical pyrylium ions can be synthesized in a single step reaction. As a result, very few derivatives of pyrylium salts are commercially available and are priced at exorbitant rates even for milligram quantities. These consequences inspired us to develop an approach for the synthesis of triarylpyrylium ion through the IEDDA reaction (Scheme 1c).

Over the years, the IEDDA reaction has gathered a remarkable amount of attention by offering a broad spectrum of applications in organic synthesis, and polymer and material science.¹³ In the life sciences, IEDDA has solved challenging problems in bioorthogonal and metal-free click chemistry.¹⁴ Following the initial success of the IEDDA of 3,6-disubstituted 1,2,4,5-tetrazines, a wide variety of tetrazines and triazines have been well investigated along with the less reactive 1,2-diazines.¹³⁻¹⁷ However, other than azine chemistry, the IEDDA has not been generalized for other substrates, especially with unprotected and non-activated substrates under mild reaction conditions.





BF₄ Symmetrical pyrylium ion

BF₄

Symmetrical pyrylium ion

R₁

---- b

Interdisciplinary Science and Technology (NIIST), Thiruvananthapuram – 695 019, India. E-mail: drsasidharbs@niist.res.in

^b Academy of Scientific and Innovative Research (AcSIR), CSIR-NIIST campus, Thiruvananthapuram 695 019, India

 $[\]dagger$ Electronic supplementary information (ESI) available: Experimental procedures, optimization table, ¹H and ¹³C NMR spectra of all new compounds (PDF), X-ray crystal structure data of **3f** (CIF). CCDC 1574744. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc06444j



Therefore, the present protocol is an effective tool for the utilization of readily available simple substrates leading to a diverse array of symmetrical and unsymmetrical pyrylium ions through the IEDDA reaction.¹⁸

In line with our previous results on the reactivity of α,β -unsaturated ketones,¹⁹ we perceived a reaction between chalcone and phenylacetylene in a nonpolar solvent, anticipating the formation of a 4H-pyran ring which can be air oxidized to a pyrylium ion. Our investigation commenced with the reaction of 0.11 mmol of chalcone (1a) and 0.33 mmol of phenylacetylene (2a) by employing 3 equivalent of $BF_3 \cdot OEt_2$ as a catalyst in CCl₄ at room temperature, a yellow colour fluorescent product (3a) precipitated out in 35% yield without any further purification. Product 3a was fully characterised by various spectroscopic techniques such as ¹H, ¹³C and ¹⁹F NMR, as well as single-crystal X-ray analysis (Scheme 2), confirming the product as 2,4,6-triphenylpyrylium tetrafluoroborate unambiguously (for details see ESI⁺). To optimise the reaction conditions, a systematic screening of various nonpolar solvents such as *n*-hexane, cyclohexane, and toluene, as well as polar solvents like THF, CH₂Cl₂, CHCl₃, DMF and ethylacetate was carried out (Table S1, ESI[†]). A comparatively higher percentage of products precipitated in nonpolar solvents than in polar solvents. In particular, 35 and 34% yields were obtained in CCl₄ and cyclohexane, respectively. For further optimisation studies we took cyclohexane as the solvent. Addition of additives like In(OTf)₃, CF₃COOH, AuCl·PPh₃, AuCl₃·3H₂O, and Cu(OAc)₂ did not improve the reaction yield. Interestingly, supply of molecular oxygen at room temperature improved the yield of the reaction to 44%. Here, oxygen is expected to act as a co-oxidant for the improved kinetics of the reaction. Further increase in the yield up to 65% was observed when the reaction was carried out at elevated temperatures (60–70 °C). In contrast, the refluxing temperature suppressed the yield of the product. Similarly, in a stoichiometric ratio of 1:2 of chalcone and phenylacetylene at 60–70 °C, pyrylium ion was obtained with a reduced yield of 49%. Furthermore, catalyst loading higher than three equivalents of BF₃·OEt₂ did not produce any encouraging result.

After optimising the reaction conditions, we explored the scope of the reaction for the synthesis of both symmetrical and unsymmetrical 2,4,6-triarylpyrylium ions using an array of chalcones and alkynes (Scheme 2).

A wide range of aromatic and heteroaromatic chalcones (1), and alkynes (2) bearing electron withdrawing, or donating groups were employed as suitable substrates. The reaction conditions showed very good functional group tolerability. Only comparable differences have been found for all the cases. From these results we concluded that aryl rings with electron donating groups are competing better in the reaction than electron withdrawing groups. But, chalcones with a -F substituent have shown higher yields than those with an electron donating group. Chalcones with heteroaryl substitution, like furan, thiophene etc. afforded higher yields. Encouraging results were also obtained with substituents -OMe, -OH, -Cl, -Br, naphthalene etc. When we extended the reaction for a fused system, using tetralone chalcone, cyclised product 3r was obtained in 57% yield. In contrast, for 2-benzylidene cyclohexanone the product 3s precipitated in a trace amount. For understanding the mechanism of the reaction we extended the scope to various substituted aryl and heteroaryl acetylenes (Scheme 3). As predicted it clearly displayed the electronic effect of substituents on the reaction process. Phenylacetylene with electron withdrawing groups reduced the yield of the reaction, while methyl and n-propyl substitution provided comparatively higher yields. 3-Ethynylthiophene afforded



Scheme 3 Scope of the reaction with substituted phenylacetylene.





the highest yield of 98%. We have also synthesized a variety of differently substituted unsymmetrical 2,4,6-triarylpyrylium ions (Scheme 4). To the best of our knowledge the present work is the first report on the synthesis of both symmetrical and unsymmetrical pyrylium ions *via* one-pot transformation.

Based on the results, we propose an inverse electron demand Diels-Alder (IEDDA) mechanism for the reaction (Scheme S7, ESI[†]). In a normal [4+2] cycloaddition, the highest occupied molecular orbital (HOMO) of the chalcone interacts with the lowest unoccupied molecular orbital (LUMO) of the arylacetylene (Fig. 1a), while coordination of BF₃ to the carbonyl lowers the energy of the LUMO of the chalcone and promotes the interaction between that and the HOMO of the arylacetylene (Fig. 1b). Density functional theory calculations²⁰ at M06-2X/SMD/6-311++G(d,p)// M06-2X/6-311++G(d,p) level (ESI^{\dagger}) show LUMO activation²¹ of the chalcone that facilitates an IEDDA mechanism. The activation energy (E_{act}) determined from transition state 1 (ts1) for this mechanism is 13.3 kcal mol⁻¹, which yields 2,4,6-triaryl-4Hpyran (Fig. 2a). Formation of the isomer 2,4,5-triaryl-4H-pyran *via* ts1' is more energy demanding ($E_{act} = 23.9 \text{ kcal mol}^{-1}$), which in fact corroborates the high regioselectivity of the reaction (Fig. S65, ESI[†]). For normal cycloaddition, without the mediation of BF₃·OEt₂, transition states similar to ts1 and ts1' show substantially higher E_{act} , viz. 26.3 and 26.8 kcal mol⁻¹, respectively (Fig. S66 and S67, ESI[†]) which confirms that BF₃·OEt₂ acts as a catalyst and brings regioselectivity in the reaction. The intermediate obtained from ts1 is 2,4,6-triaryl-4*H*-pyran···BF₃ adduct (Fig. 2b). BF₃ in the adduct showed a strong tendency to abstract the hydride moiety from the saturated C-H bond by heterolytically cleaving it with E_{act} 30.2 kcal mol⁻¹ via ts2 (Fig. 2c). This step of the



Fig. 2 (a-c) Optimised geometries. (d) Energy profile. All bond lengths in Å.

reaction yields the ion-pair complex of pyrylium cation and BF_3H^- . The BF_3H^- may further react with BF_3 in the system to yield BF_4^- , the counter cation observed in the crystal structure of **3f** (Scheme 2). This also supports the use of an excess amount of BF_3 in the reaction. The pyrylium cation formation from 4*H*-pyran is endothermic because the bond energy of the cleaved C-H bond is very high compared to the newly formed ionic B-H bond (Fig. 2d). Although the facile nature of the reaction under mild conditions cannot be fully explained by the endothermic nature of the product formation, the conversion of BF_3H^- to BF_4^- in excess of BF_3 may drive the reaction towards the forward direction.

Since the pyrylium ions are of high industrial relevance, the production in large scale by means of a simple and industrially feasible process is highly desirable. Hence, we conducted an experiment with 1 g of 3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (1 g) and the product **3f** yielded 763 mg (43%) under the optimised conditions (Scheme 5). Alongside, a pyrylium ion with different anions shows variations in physical properties and reactivity. Hence, in an attempt to prepare pyrylium ions with triflate as the anion using triflic acid as the catalyst was successfully demonstrated with a yield of 48% (**4a**) (Scheme 5).

In conclusion, we have developed an effective protocol towards the industrially relevant pyrylium ions from simple precursors: chalcones and alkynes. The strategy provides a wide range of symmetrical as well as unsymmetrical triarylpyrylium



Fig. 1 Frontier molecular orbital interaction for [4+2] cycloaddition (a) without and (b) with BF_3 mediation.



Scheme 5 (a) Gram-scale synthesis of **3f**. (b) Synthesis of 2,4,6-triphenylpyrylium triflate, **4a**.

ions through operationally simple and mild reaction conditions in one-pot. The reaction proceeds *via* a highly regioselective inverse electron demand Diels–Alder (IEDDA) mechanism. Ongoing efforts in our laboratory are directed toward the establishment of the generality of this protocol on other heterocyclic appended and fused chalcone systems for the exploration of catalytic and photophysical properties.

Financial support from the DST-Science & Engineering Research Board (SERB), Government of India (Grant no. EEQ/ 2016/000089) is gratefully acknowledged. C. T. F. S. thanks UGC for a research fellowship.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- (a) A. T. Balaban, in Pyrylium Salts as Useful Synthesis in Organic Synthesis: Modern Trends (Proc. 6th IUPAC Internat. Symp. on Organic Synthesis, Moscow), ed. O. Chizov, Blackwell, Oxford, 1987, pp. 263–274;
 (b) M. A. Miranda and H. Garcia, Chem. Rev., 1994, 94, 1063–1089;
 (c) T. Okamoto, N. Yamamoto and M. Kawaguchi, EP0659407B1, 2001.
- 2 (a) A. T. Balaban and C. Toma, *Tetrahedron*, 1966, 22, 1–8; (b) A. T. Balaban, *Tetrahedron*, 1968, 24, 5059–5065; (c) A. T. Balaban, *Tetrahedron*, 1970, 26, 739–742; (d) J. D. Tovar and T. M. Swager, *J. Org. Chem.*, 1999, 64, 6499–6504; (e) C. Müller, D. Wasserberg, J. J. M. Weemers, E. A. Pidko, S. Hoffmann, M. Lutz, A. Spek, S. C. J. Meskers, R. A. J. Janssen, R. A. V. Santen and D. Vogt, *Chem. Eur. J.*, 2007, 13, 4548–4559; (f) A. R. Katritzky, *Tetrahedron*, 1980, 36, 679–699.
- 3 E. Alfonzo, F. S. Alfonso and A. B. Beeler, Org. Lett., 2017, 19, 2989–2992.
- 4 G. A. Reynolds and J. A. V. Allan, US Pat., 3417083, 1968.
- 5 J. W. Ammons, P. B. Mauer, G. A. Reynolds and J. A. V. Allan, *US Pat.*, 3462706, 1969.
- 6 (a) F. P. Schafer, W. Schmidt and K. Marth, *Phys. Lett. A*, 1967, 24, 280–281; (b) G. A. Reynolds and K. H. Drexhage, *J. Org. Chem.*, 1977, 42, 885–888; (c) T. Kotowski, W. Skubiszak, J. A. Soroka, K. B. Soroka and T. Stacewicz, *J. Lumin.*, 1991, 50, 39–45; (d) J. Zhang and Z. Zhu, *Dyes Pigm.*, 1995, 27, 263–269; (e) M. Fakis, J. Polyzos, G. Tsigaridas, J. Parthenios, A. Fragos, V. Giannetas, P. Persephonis and J. Mikroyannidis, *Chem. Phys. Lett.*, 2000, 323, 111–116.
- 7 (a) A. M. Bonch-Bruevich, E. N. Kaliteevskaya, T. K. Razumova, A. D. Roshal and A. N. Tarnovski, *Opt. Spectrosc.*, 2000, **89**, 216–224;
 (b) P. Nikolov and S. Metzov, *J. Photochem. Photobiol.*, *A*, 2000, **135**, 13–25.

- 8 (a) G. A. Reynolds, J. A. V. Allan and L. E. Contois, US Pat., 3938994, 1976; (b) C. W. Tang, US Pat., 4164431, 1979; (c) T. Maeda, S. Nitta, H. Nakao, S. Yagi and H. Nakazumi, J. Phys. Chem. C, 2014, 118, 16618–16625.
- 9 (a) W. J. Dilthey, Pr. Chem., 1916, 94, 53–76; (b) J. A. Vanalla and G. A. Reynolds, J. Org. Chem., 1968, 33, 1102–1105; (c) A. Dinculescu, T. S. Balaban, C. Popescu, C. D. Toadera and A. Balaban, Bull. Soc. Chim. Belg., 1991, 100, 665–672.
- 10 (a) W. C. Dovey and R. Robinson, J. Chem. Soc., 1935, 1389–1390; (b) A. R. Katritzky and S. S. Thind, J. Chem. Soc., Perkin Trans. 1, 1980, 1895–1900.
- 11 H. J. T. Bos and A. F. Arens, Recl. Trav. Chim. Pays-Bas, 1963, 82, 845–858.
- (a) G. L. Ning, X. C. Li, M. Munakata, W. T. Gong, M. Maeka-wa and T. Kamikawa, J. Org. Chem., 2004, 69, 1432–1434; (b) L. Yang, J. Ye, Y. Gao, D. Deng, W. Gong, Y. Lin and G. Ning, Tetrahedron Lett., 2013, 54, 2967–2971.
- 13 (a) A. Palasz, *Top. Curr. Chem.*, 2016, 374, 24; (b) A. C. Knall and C. Slugovc, *Chem. Soc. Rev.*, 2013, 42, 5131–5142; (c) Z. M. Png, H. Zeng, Q. Ye and J. Xu, *Chem. Asian J.*, 2017, 12, 2142–2159; (d) X. Liu, H. Zheng, Y. Xia, L. Lin and X. Feng, *Acc. Chem. Res.*, 2017, 50, 2621–2631.
- 14 (a) T. Plass, S. Milles, C. Koehler, J. Szymanski, R. Mueller, M. Wießler, C. Schultz and E. A. Lemke, *Angew. Chem., Int. Ed.*, 2012, 51, 4166–4170; (b) K. Lang, L. Davis, S. Wallace, M. Mahesh, D. J. Cox, M. L. Blackman, J. M. Fox and J. W. Chin, *J. Am. Chem. Soc.*, 2012, 134, 10317–10320; (c) C. S. McKay and M. G. Finn, *Chem. Biol.*, 2014, 21, 1075–1101; (d) K. Lang and J. W. Chin, *ACS Chem. Biol.*, 2014, 9, 16–20.
- 15 E. M. Sletten and C. R. Bertozzi, Angew. Chem., Int. Ed., 2009, 48, 6974–6998.
- 16 C. P. Ramil and Q. Lin, Chem. Commun., 2013, 49, 11007-11022.
- 17 H. Wu and N. K. Devaraj, Top. Curr. Chem., 2016, 374, 3.
- 18 Patent filed: C. T. F. Salfeena, B. S. Sasidhar and A. Ajayaghosh, Process for the preparation of pyrylium salts, Application No. 201811004385, Dated: 16-02-2018.
- 19 (a) C. T. F. Salfeena, K. T. Ashitha and B. S. Sasidhar, Org. Biomol. Chem., 2016, 14, 10165–10169; (b) K. T. Ashitha, V. P. Kumar, C. T. F. Salfeena and B. S. Sasidhar, J. Org. Chem., 2018, 83, 113–124; (c) C. T. F. Salfeena, R. Jalaja, R. Davis, E. Suresh and S. B. Somappa, ACS Omega, 2018, 3, 8074–8082.
- 20 (a) M. J. Frisch, et al., Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford CT, 2009; (b) C. J. Cramer and D. G. Truhlar, Phys. Chem. Chem. Phys., 2009, 11, 10757–10816; (c) K. Raghavachari, J. S. Binkley, R. Seeger and J. A. Pople, J. Chem. Phys., 1980, 72, 650–654; (d) Y. Zhao and D. G. Truhlar, J. Chem. Phys., 2006, 125, 194101; (e) K. Remya and C. H. Suresh, J. Comput. Chem., 2013, 34, 1341–1353; (f) A. V. Marenich, C. J. Cramer and D. G. Truhlar, J. Phys. Chem. B, 2009, 113, 6378–6396; (g) G. Scalmani and M. G. Frisch, J. Chem. Phys., 2010, 132, 114110.
- 21 X. Jiang and R. Wang, Chem. Rev., 2013, 113, 5515-5546.