Visible light promoted thiol-ene reactions using titanium dioxide†

Venugopal T. Bhat, Petar A. Duspara, Sangwon Seo, Nor Syazwani Binti Abu Bakar and Michael F. Greaney*

The radical addition of thiols to alkenes is reported under photoredox conditions, using visible light and TiO₂ as a cheap and readily available photocatalyst.

Recent developments in visible light photoredox catalysis (PRC) have substantially expanded the scope and application of organic photochemistry. Using a domestic lightbulb as the light source, rather than specialist UV equipment, the process uses a photoactive catalyst to mediate electron transfer between reactants, resulting in novel transformations that frequently proceed under mild conditions. The vast majority of PRC in organic synthesis to date is based on two classes of catalyst; transition metal complexes, such as the archetypal Ru(bpy)₃Cl₂ and Ir(ppy)₃ systems, or organic dyes such as methylene blue or eosin-Y. The Noble metals of the first class are expensive and a limited resource, but are highly optimisable in terms of ligand-metal tuning. Organic dyes lack this particular quality, but may be tuned via conventional synthesis and are usually less expensive. We were interested in exploiting a third class of photoredox catalyst; semi-conducting metal oxides such as titania (TiO₂). With 4 million tons of titania being produced per annum, the material is cheap, readily accessible, and non-toxic (commonly ingested as food additive E 171), as well as offering the process benefits of heterogeneous catalysis such as simple removal by filtration. The UV photoredox properties of TiO₂ have been extensively investigated and applied on an industrial scale to areas such as water treatment and photovoltaics. Applications to organic synthesis, however, remain under-developed, particularly in the area of visible light photochemistry. We were interested in developing a titania-mediated PRC reaction using visible light, and chose to investigate the thiol-ene reaction for this purpose.

The addition of thiols to alkenes is a radical reaction that is typically initiated with UV light. Although an old reaction, its reliability, substrate scope, and compatibility has led to renewed interest in the context of click chemistry, where the facile C–S bond formation can be used as a powerful ligation strategy in biological and materials science. Indeed, the largest field of application for thiol-ene chemistry is currently in polymer science, where thiols are cross-linked with alkenes under UV curing conditions, producing polymers with very uniform step-growth properties. Recent literature reports have established PRC for thiol-ene addition using both Ru(II) and eosin-Y photocatalysis, providing an important frame of reference for our inchoate titania process.

We were aware at the outset that titania visible light PRC would likely require a nanoparticulate form of the catalyst. Unmodified titania absorbs very weakly in the visible region, but there is evidence that substrate binding to the surface can shift the absorption and enable electron transfer. Rueping and co-workers, for example, have recently demonstrated...

| Entry | TiO₂ (equiv.) | Solvent | Light source | Yield (%) |
|-------|---------------|---------|--------------|-----------|
| 1     | 1.0           | MeCN    | 20 W light   | 98 (96*)  |
| 2     | 1.0           | DCM     | 20 W light   | 96        |
| 3     | 1.0           | —       | 20 W light   | 97        |
| 4     | 1.0           | MeCN    | Blue LED     | 80        |
| 5     | 1.0           | MeCN    | No light     | 0         |
| 6     | 0             | MeCN    | 20 W light   | 20        |
| 7     | 0             | MeCN    | Blue LED     | 0         |
| 8     | 0.5           | MeCN    | 20 W light   | 88        |
| 9     | 0.1           | MeCN    | 20 W light   | 82        |
| 10    | 0.1           | MeCN    | 20 W light   | 92        |
| 11    | 1.0           | MeCN    | 20 W light   | 50        |
| 12    | 1.0           | MeCN    | 20 W light   | 84        |

*a Cyclohexene (1.0 mmol), benzyl mercaptan (4.0 mmol), titania (TiO₂ P25) and solvent (1.0 mL) at room temperature for 16 h; light source placed 10–15 cm away from reaction vials. † Yields determined by ¹H NMR using nitromethane as the internal standard. ‡ Isolated yields. § Foil-wrapped flask for 16 h. † Reaction for 40 h. § Using degassed MeCN under N₂ atmosphere. ¶ Using 2.5 mmol of benzyl mercaptan.
visible light photoredox activity in dehydrogenative coupling reactions using commercially available titania P25 nanoparticles, and we chose to begin our studies using this material (aeroxide from Sigma-Aldrich). Using the addition of benzyl mercaptan (1a) to cyclohexene (2a) as a test reaction, we were pleased to observe very high conversions into adduct 3a using one equivalent of TiO2 in MeCN under irradiation with a domestic light bulb (Table 1). The reaction was also viable in DCM (entry 2), under neat conditions (entry 3), and using blue LEDs as an alternative light source (entry 4).

Control experiments established that titania in the dark gave no reaction (entry 5), but there was a small background reaction with ambient light in the absence of titania (20% conversion). We were pleased to see that the titania loading could be reduced to catalytic quantities with little drop in overall yield (entries 8–10), and we established that oxygen was beneficial for the reaction. Use of an inert atmosphere and degassed solvent halved the efficiency of the process (entry 11). This was an expected requirement, as an oxidative quencher is needed to balance charge and prevent hole-electron recombination in the titania photocatalyst (vide infra).

With a titania PRC system in place, we moved on to investigate substrate scope, beginning with the alkene partner. We were pleased to find that a variety of primary and 1,1-disubstituted substrates underwent successful thiol-ene reaction with benzyl mercaptan (Table 2). The reaction was tolerant of a variety of functional groups (ester, alcohol, silane, nitrile, halogen) giving the thiol ene adducts 3 in generally high yields. Substitution was

| Table 2 | Scope of alkene coupling partnersa |
|---------|----------------------------------|
| Entry   | Alkene | Product | Yieldb (%) |
| 1       | 2b OMe | 3b      | 85 (9)     |
| 2       | 2c OAc | 3c      | 75 (61)    |
| 3       | 2d Me  | 3d      | 78 (12)    |
| 4       | 2e CH3 | 3e      | 89 (68)    |
| 5       | 2f Sm | 3f      | 97 (31)    |
| 6       | 2g CN  | 3g      | 43 (0)     |
| 7       | 2h OAc | 3h      | 80 (0)     |
| 8       | 2i     | 3i      | 98 (90)    |
| 9       | 2j     | 3j      | 98 (93)    |
| 10      | 2k     | 3k      | 95 (30)    |

a) Alkene (1.0 mmol), benzyl mercaptan (4.0 mmol), titania (TiO2 P25, 1.0 mmol) and MeCN (1.0 mL) at room temperature for 16 h; light source placed 10–15 cm away from reaction vials. b) Isolated yields; numbers in parentheses are the yield obtained under standard reaction conditions where titanium dioxide is absent.

| Table 3 | Catalytic thiol-ene – thiol scopea,b |
|---------|------------------------------------|
| Entry   | Thiol | Product | Yieldd (%) |
| 1       | 1b    | 3l      | 86 (0)     |
| 2       | 1c    | 3m      | 79 (8)     |
| 3       | 1d    | 3n      | 87 (30)    |
| 4       | 1e    | 3o      | 61 (14)    |
| 5       | 1f    | 3p      | 30 (5)     |
| 6       | 1g    | —       | 0          |
| 7       | 1h    | 3q      | 68 (0)     |
| 8       | 1i    | 3r      | 73 (0)     |
| 9       | 1j    | 3s      | 70 (0)     |
| 10      | 1k    | 3t      | 57 (0)     |

a) Thiol (4.0 mmol), vinyl acetate (1.0 mmol), titania (TiO2 P25, 0.1 mmol) and MeCN (1.0 mL) at room temperature for 16–40 h; light source placed 10–15 cm away from reaction vials. b) Dithiol (1 mmol), styrene (4 mmol) and conditions as previous. c) Isolated yields; numbers in parentheses are the yield obtained under standard reaction conditions where titanium dioxide is absent. d) 1 equiv. of titania used.
tolerated at the 2- and 3-positions of the alkene (entries 3 and 4), but 1,2-disubstitution was restricted to cyclic alkenes. Vinyl acetate and acrylonitrile were both productive, interestingly undergoing no reaction at all in the absence of PRC (entries 6 and 7). More reactive alkenes such as styrenes gave very high yields of the thiolene products, but background reaction was high for alkene (entries 7–9).

Thiol scope was initially trialled (Table 3) using catalytic amounts of titania (0.1 equiv.) and vinyl acetate (2h), an alkene with zero background reaction for the addition of benzyl mercaptan (Table 1, entry 7). We were pleased to find that the catalytic protocol was successful, with primary alkyl thiols (entries 1–3) and thiophenols (entry 4) undergoing thiolene reaction under the longer reaction time of 40 h. Increasing steric hindrance around the thiol was deleterious, with cyclohexyl thiol reacting in moderate yield (entry 5) and tert-butyl thiol undergoing no reaction, even with stoichiometric titania (entry 6). We could extend the reaction to a double thiolene reaction, with ethane and propane dithiol undergoing addition to thiorenes in good yield (entries 7–9). p-Methoxy styrene proved less reactive, and required stoichiometric quantities of titania to yield 3t in an acceptable timeframe.

A mechanism for the reaction is outlined in Scheme 1, based upon the photo-excitation of electrons to the conduction band of the titania catalyst. The resultant holes are reductively quenched by the thiol, generating a thyl radical cation, which can lose a proton to give a thyl radical. Oxygen acts as a sacrificial electron acceptor, enhancing reaction efficiency by reducing hole-electron recombination in the titania. The thyl radical can then initiate the thiolene cycle through addition to an alkene and generation of an alkyl radical, which propagates the reaction by abstracting a hydrogen atom from the thyl starting material.

In conclusion, we have developed a titania photoredox system for the thiolene reaction that uses visible light. The photocatalyst is cheap, robust, readily available, and easily processed out of the reaction for re-use. Applications of this method to the broad remit of thiolene chemistry are ongoing in our laboratory.

We thank the University of Manchester and the EPSRC for funding.

Notes and references

1 Recent reviews: (a) J. M. R. Narayanan and C. R. J. Stephenson, Chem. Soc. Rev., 2011, 40, 102–113; (b) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, Chem. Rev., 2013, 113, 5322–5363; (c) S. Fukuzumi and K. Ohkubo, Org. Biomol. Chem., 2014, 12, 6059–6071; (d) D. P. Hart and B. König, Chem. Commun., 2014, 50, 6688–6699; (e) M. N. Hopkinson, B. Sahoo, J. L. Li and F. Glorius, Chem. – Eur. J., 2014, 20, 3874–3886; (f) D. A. Nicewicz and T. M. Nguyen, ACS Catal., 2014, 4, 355–360.

2 (a) C. Chen, W. Ma and J. Zhao, Chem. Soc. Rev., 2010, 39, 4206–4219; (b) P. Roy, S. Berger and P. Schmuki, Angew. Chem., Int. Ed., 2011, 50, 2904–2939; (c) B. O’Regan and M. Grätzel, Nature, 1991, 353, 737–740.

3 Selected examples of UV titania photoredox catalysis: (a) C. M. Wang and T. E. Mallouk, J. Am. Chem. Soc., 1990, 112, 2016–2018; (b) C. W. Lai and T. E. Mallouk, Chem. Commun., 1993, 1359–1361; (c) H. Arada, R. Kawakatsu, N. Fujiwara and M. Matsumura, Chem. Commun., 2006, 2804–2806; (d) X. J. Lang, H. W. Ji, C. C. Chen, W. H. Ma and J. C. Zhao, Angew. Chem., Int. Ed., 2011, 50, 3934–3937; (e) D. W. Manley, R. T. McBurry, P. Miller, R. F. Howe, S. Rydherd and J. C. Walton, J. Am. Chem. Soc., 2012, 134, 13580–13583; (f) D. W. Manley, R. T. McBurry, P. Miller and J. C. Walton, J. Org. Chem., 2014, 79, 1386–1398; (g) D. W. Manley and J. C. Walton, Org. Lett., 2014, 16, 5394–5397.

4 With visible light: (a) F. Pariroo, A. Ramakrishnan and H. Kisch, Angew. Chem., Int. Ed., 2008, 47, 7107–7109; (b) M. Cherevatskaya, M. Neumann, S. Fuldner, C. Harlander, S. Kummel, S. Danksreiter, A. Pfitizer, K. Zeiterl and B. König, Angew. Chem., Int. Ed., 2012, 51, 4062–4066; (c) X. Lang, W. Ma, Y. Zhao, C. Chen, H. Ji and J. Zhao, Chem. – Eur. J., 2012, 18, 2624–2631; (d) M. Rueping, J. Zoller, D. C. Fabry, K. Poschary, R. M. Koening, T. E. Weirich and J. Mayer, Chem. – Eur. J., 2012, 18, 3476–3481; (e) C. Villa and M. Rueping, Green Chem., 2013, 15, 2056–2059; (f) C. D. McTernan, S. P. Hite, H. Ismaill and J. C. Scaino, Adv. Synth. Catal., 2014, 356, 2819–2824.

5 F. Denés, M. Pichowicz, G. Povie and P. Renaud, Chem. Rev., 2014, 114, 2587–2693.

6 T. Posner, Ber. Dtsch. Chem. Ges., 1905, 38, 646–657.

7 C. E. Hoyle and C. N. Bowman, Angew. Chem., Int. Ed., 2010, 49, 1540–1573.

8 (a) R. S. Lowe, Polym. Chem., 2014, 5, 4820–4870; (b) N. Brummelhuis, C. Diehl and H. Schlaad, Macromolecules, 2008, 41, 9946–9947; and references therein.

9 (a) E. L. Tyson, M. S. Ament and T. P. Yoon, J. Org. Chem., 2013, 78, 2046–2050; (b) E. L. Tyson, Z. L. Niemeyer and T. P. Yoon, J. Org. Chem., 2014, 79, 1427–1436.

10 M. H. Keylor, J. E. Park, C.-J. Wallentin and C. R. J. Stephenson, Tetrahedron, 2014, 70, 4264–4269.

11 (a) C. A. DeFores and K. S. Anseth, Nat. Chem., 2011, 3, 925–931; (b) C. A. DeFores and K. S. Anseth, Angew. Chem., Int. Ed., 2012, 51, 1816–1819; (c) H. Shih and C. C. Lin, Macromol. Rapid Commun., 2013, 34, 269–273; (d) H. Shih, A. K. Fraser and C. C. Lin, ACS Appl. Mater. Interfaces, 2013, 5, 1673–1680.