

Transition Metal-Free, Visible Light-Mediated Radical Cyclisation of Malonyl Radicals onto 5-Ring Heteroaromatics

Pol Hernández-Lladó,^a Kilian Garrec,^a Daniel C. Schmitt,^b Jonathan W. Burton^{*a}

^a Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK. E-mail: jonathan.burton@chem.ox.ac.uk

^b Medicine Design, Pfizer Worldwide Research, Development and Medical, Groton, Connecticut 06340, United States

Received: ((will be filled in by the editorial staff))



Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.201#####>. ((Please delete if not appropriate))

Abstract. Annulated heteroaromatics can be accessed through the addition of malonyl radicals onto heterocycles. Current methods are applicable to electron-rich heteroaromatics and reliant on transition metals or toxic tin reagents. Here we report a metal-free, visible light-mediated cyclisation of malonates onto 5-ring heteroaromatics using iodomalones as key intermediates.

The iodomalones are prepared and photolysed *in situ* to give the desired annulated products, in yields of 46–94% without the need for external catalysts. The scope of this transformation includes *N*-alkyl, *N*-acyl and carbon-tethered malonates adding onto a wide range of 5-membered heteroaromatics.

Keywords: photochemistry, radical reactions, annulation, heterocycles, synthetic methods

Introduction

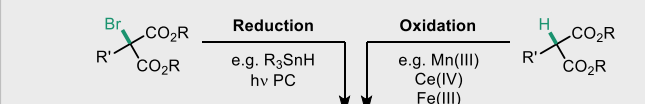
Annulated heteroaromatics are common structural motifs both in nature and medicinal chemistry,^[1] examples being the marketed drugs ketorolac and frovatriptan, as well as numerous alkaloids including vincamine (Scheme 1D).^[2–4] These partially saturated ring systems are often built through heterocycle ring-forming reactions, such as cyclocondensations,^[2–3] but can also be prepared through cyclisation reactions onto pre-existing heteroaromatics (Scheme 1A). Within this latter synthetic framework there have been several reports of the cyclisation of carbon-centred radicals onto unsaturated heterocycles involving nucleosides and/or nucleotides.^[5–6] From the 1990s, the field expanded rapidly with reports of cyclisations of alkyl, acyl, vinyl, aryl, and malonyl radicals onto a variety of heterocycles including pyridines/pyridinium ions,^[7–10] indoles,^[11–22] pyrroles,^[13, 16, 21–28] imidazoles,^[26, 28–29] triazoles,^[30] thiophenes,^[14, 22] and pyrazoles^[31] to form fused five, six, and seven-membered rings. Many of these methods used organotin reagents with most studies reporting cyclisations onto a small number of electronically similar heteroaromatics. In the past two decades, further methods for radical cyclisations onto heteroarenes have been developed with annulations that bypass the need for tin reagents including those using peroxides^[32–35] as well as light-mediated annulations^[36–40] being disclosed. Malonyl radicals

have frequently been used in (hetero)arene annulation^[37, 41–43] likely due to their ready formation coupled with straightforward product derivatisation.

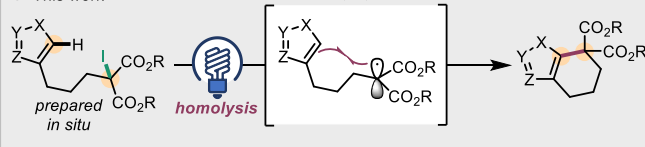
A. Approaches to annulated heteroaromatics



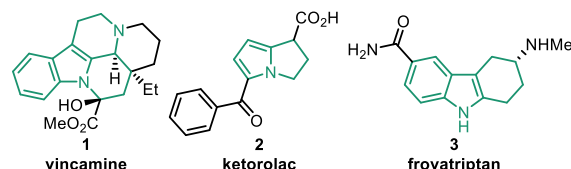
B. Previous malonyl radical generation methods



C. This work



D. Examples of compounds containing annulated heteroaromatics



Scheme 1. Approaches to annulated heteroaromatics, malonyl radical generation methods, and examples of compounds containing such motifs (PC = photocatalyst).

Malonyl radicals are generally formed from halomalonates either by reduction with an organostannane radical or using light and an appropriate photocatalyst,^[36, 44–46] by photolysis of halomalonates often in the presence of an organostannane,^[37, 47–49] or by oxidation of malonates frequently with transition metal salts such as those based on Mn(III),^[50] Ce(IV)^[41, 50d, 51] and Fe(III) (Scheme 1B).^[41, 50d, 52] Despite the variety of malonyl radical generation methods, malonyl radical cyclisations onto four of the most common ring systems in small molecule drugs: imidazoles, thiazoles, isoxazoles, and pyrazoles have little precedence.^[53] Given the prevalence and importance of annulated heterocycles both in natural products and drug targets, we sought to develop a metal-free cyclisation of malonyl radicals for the formation of a range of annulated heterocycles. Herein we report a transition-metal free visible-light mediated cyclisation of malonates onto 5-ring heteroaromatics (Scheme 1C).^[37, 54] Examples of cyclisations onto a wide range of heteroaromatic substrates are reported (including indole, pyrrole, imidazole, triazole, isoxazole, thiophene, thiazole, benzothiophene, benzofuran, azaindole, deazapurine, and xanthine) and the utility of the methodology is demonstrated in the synthesis of the anti-inflammatory drug ketorolac.^[55]

Results and Discussion

We initiated our studies with the cyclisation of indole **4**, a common substrate in previously reported malonyl radical cyclisations.^[36] Our aim was to develop a procedure for the formation of the annulated product **5** via a one-pot iodination and subsequent cyclisation. Initial reaction conditions involved deprotonation of **4** with NaHMDS at -78°C , followed by addition of *N*-iodosuccinimide (NIS). After 5 h in the dark, 2,6-lutidine was added and the mixture irradiated with a 30 W white compact fluorescent light (CFL). These conditions gave desired product **5** in 51% yield together with 30% of cyclopropane **6** (entry 1, Table 1).^[56] Table 1 summarises the reaction optimisation that followed (see Supporting Information S131 for full details). NaHMDS provided the best yield of **5** compared with LiHMDS, KHMDS, NaH and *t*BuOK (entries 2–5, Table 1), while the presence of 2,6-lutidine had no effect (entries 1, 6, Table 1). Reversing the order of addition, i.e. adding NaHMDS to a mixture of NIS and malonate, minimised the formation of cyclopropane **6** (entry 7, Table 1). Under these conditions, product **5** was obtained in an excellent 94% yield. This reaction was equally effective on a 1.0 mmol scale (entry 8, Table 1). THF was the best solvent following a brief solvent screen (see Supporting Information S131). Control experiments showed no formation of indole **5** occurred in the dark or when replacing NIS for NCS or NBS in keeping with previous reports^[36] (entries 9–11, Table 1). In the presence of TEMPO neither **5** nor **6** were produced, consistent with a radical-based mechanism for the cyclisation. Rather, the product of trapping of a

malonyl radical derived from **4** with TEMPO was formed (entry 12, Table 1, see Supporting Information S18–19 for characterisation of TEMPO adducts from **4** and **29**).

Table 1. Optimisation of the cyclisation of indole **4**.

Entry	Deviation from above	Scale [mmol]	Yield of 5 ^{a)}	Yield of 6 ^{a)}
1	—	0.05	51%	30%
2	LiHMDS	0.05	38%	58%
3	KHMDS	0.05	12%	0%
4	NaH	0.05	39%	8%
5	<i>t</i> BuOK	0.05	37%	<5%
6	No 2,6-lutidine	0.05	58%	28%
7 ^{b)}	No 2,6-lutidine	0.20	94% ^{c)}	<5%
8 ^{b)}	No 2,6-lutidine	1.0	94% ^{c)}	<5%
9 ^{b)}	No light	0.05	0%	0%
10	NCS instead of NIS	0.05	0%	13%
11	NBS instead of NIS	0.05	0%	51%
12 ^{b)}	No 2,6-lutidine + 1.1 equiv. TEMPO	0.20	0%	0%

a) Calculated yield by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard; b) NaHMDS added over 30 min at -78°C ; c) Isolated yield.

Under the optimised conditions, several *N*-alkyl and *N*-acyl tethered malonates underwent cyclisation (Table 2). The formation of cyclopropane products was specific to the *N*-acyl heteroaromatics, i.e. **4**, **7**, **13**, hence reverse addition was only used with these substrates. The iodination cyclisation of *N*-acyl malonates provided six-membered rings **5** and **14** (entries 1 and 5, Table 2) in excellent yields, while the desired five-membered ring product was not obtained from indole **7** (entry 2, Table 2). On the other hand, *N*-alkyl six-, and five-membered rings were formed in good yields with cyclisations onto indoles (entries 3 and 4, Table 2), and pyrroles (entries 6 and 7, Table 2) giving the annulated products **10**, **12**, **16**, and **18a–c**. The 6-ring annulated imidazole **24** was formed in 57% yield (entry 10, Table 2), while the corresponding five-membered product was not obtained from imidazole **25** in line with previous observations by Bowman (entry 11, Table 2).^[26] A 1,2,3-triazole substrate did not yield any annulated product (entry 12, Table 2). Pleasingly, yields were unaffected by the nature of the malonate, as exemplified by the formation of the

Table 2. *N*-acyl and *N*-alkyl reaction scope.

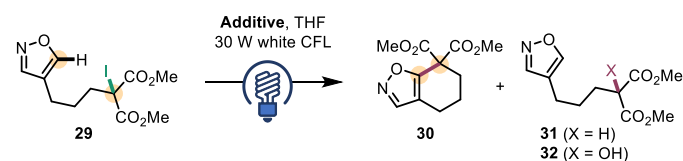
entry	substrate	product (isolated yield)
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		

Reagents and conditions: substrate (0.20 mmol), NaHMDS (1.2 equiv.), NIS (1.2 equiv.), THF (0.1 M), -78°C to RT, 5 h; then 30 W white CFL, RT, 18 h.

annulated products containing *tert*-butyl and benzyl malonates **18b**, and **18c** (entry 7, Table 2). Likewise, substitution on the pyrrole substrate was accommodated; 2-aryl pyrroles **22b**, and **22c**, were formed in good yields, as well as 2-benzoylpyrrole **22a** (entry 9, Table 2). C3-Substituted pyrrole **20** was

isolated as a single regioisomer (entry 8, Table 2), which we hypothesise is due to the increased stabilisation the carboxylate group can confer to the intermediary allylic radical. Finally, the cyclisation of indole **11** was performed on a gram-scale without major changes in the reaction set-up (1.0 g scale, 92% yield, entry 4, Table 2, see Supporting Information S130).

Encouraged by these results, we aimed to expand our methodology to a wider range of heteroarenes, including those where the tether is located on a *C*-atom in the heteroaromatic substrate. We focused on the functionalisation of azoles, which are extensively used in medicinal chemistry but unprecedented substrates for malonyl radical cyclisations. Isoxazole **29** was chosen as the substrate for optimisation. The reasons behind this were two-fold: firstly, it is prone to ring-opening, unlike many 5-ring heteroaromatics and secondly, malonate **31**, iodomalonate **29**, hydroxymalonate **32**, and desired product **30** had diagnostic ^1H NMR peaks that did not overlap. This, in conjunction with an internal standard (1,3,5-trimethoxybenzene), enabled yield measurement by ^1H NMR.

Table 3. Optimisation of the cyclisation of iodomalonate **29**.

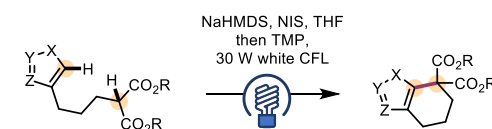
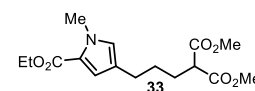
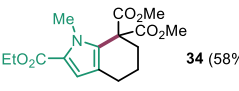
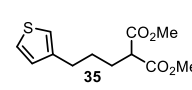
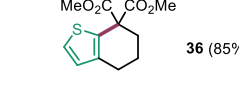
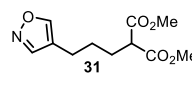
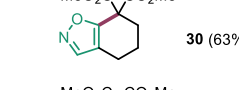
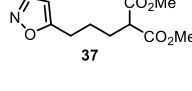
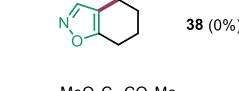
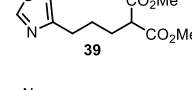
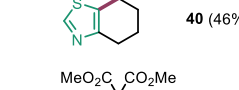
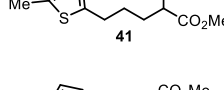
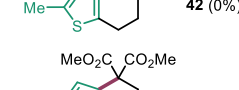
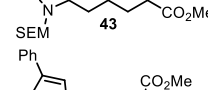
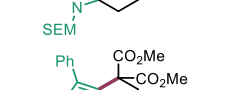
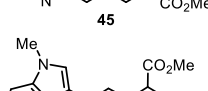
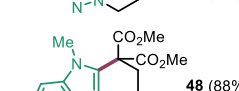
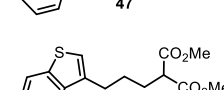
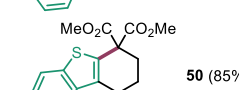
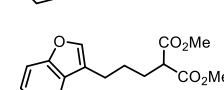
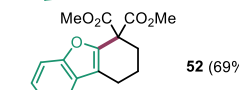
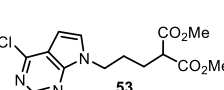
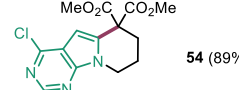
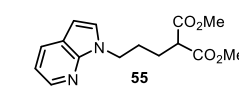
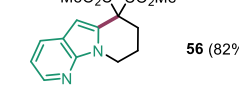
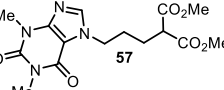
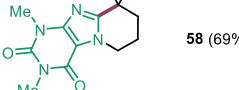
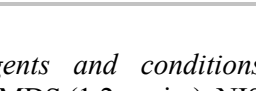
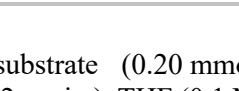
Entry	Additive	Yield of 30 ^{a)}	Yield of 31 ^{a)}	Yield of 32 ^{a)}
1	—	11%	7%	8%
2	Under air	0%	0%	43%
3	2,6-lutidine	17%	11%	22%
4	NEt ₃	4%	91%	0%
5 ^{b)}	quinuclidine	17%	37%	0%
6 ^{b)}	PMP	27%	25%	41%
7	K ₂ CO ₃	49%	12%	<5%
8	TMP	66%	12%	13%
9	TMP (2.0 equiv.)	66%	3%	29%
10	TMP (5.0 equiv.)	45%	0%	58%
11 ^{b)}	TMP (2.0 equiv.)	63% ^{d)}	0%	0%
12 ^{b,c)}	TMP (2.0 equiv.)	56% ^{d)}	0%	0%
13	TEMPO (1.0 equiv.)	0%	0%	0%

Reagents and conditions: Iodomalonate **29** (0.20 mmol), additive (1.2 equiv.), THF (0.1 M), 30 W white CFL, RT, 18 h. ^{a)} Calculated yield by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard; ^{b)} Reaction carried out on a 0.20 mmol scale; ^{c)} One-pot procedure from the corresponding malonate; ^{d)} Isolated yield.

The reaction was optimised stepwise, rather than in a one-pot fashion. The initial iodination gave iodomalonnate **29** in 76% isolated yield under our standard conditions, hence we turned our attention to its cyclisation (Table 3, see Supporting Information S132–133, for screen of bases, additives, and light sources). Upon irradiation in THF and in the absence of any base, iodomalonnate **29** gave a mixture of cyclised product **30** (11%), malonnate **31** (7%), and hydroxymalonnate **32** (8%) (entry 1, Table 3). Degassing of solvents was necessary to reduce competing formation of hydroxymalonnate **32** (entry 2, Table 3).^[49] 2,6-Lutidine had no effect in the reaction outcome (entry 3, Table 3), whereas triethyl amine, quinuclidine, and 1,2,2,6,6-pentamethylpiperidine (PMP) increased dehalogenation (entries 4–6, Table 3). This may be due to the competing formation of α -amino radicals through hydrogen atom abstraction by the malonyl radical. Indeed the use of potassium carbonate increased the yield of **30** and reduced the yield of deiodinated malonnate **31** (entry 7, Table 3). However, using 2,2,6,6-tetramethyl piperidine (TMP), a hindered secondary amine from which α -amino radicals cannot be formed, increased the yield of **30** to 66% with limited dehalogenation to yield **31** (12%) (entry 8, Table 3). The addition of 2.0 equivalents of TMP proved optimal, with **30** being isolated in 63% yield on a 0.20 mmol scale (entries 8–11, Table 3). This was transferable to the one-pot procedure, giving cyclised isoxazole **30** in comparable yields (entry 12, Table 3). Furthermore, under these optimised conditions changing the light source reduced the yield of **30** (see Supporting Information S133). As with the indole **4**, conducting the reaction in the presence of TEMPO resulted in no cyclised product being formed but rather, the product of trapping of a malonyl radical derived from **29** with TEMPO was formed (entry 12, Table 2, see Supporting Information S18–19 for characterisation of TEMPO adducts from **4** and **29**).

These new conditions were applicable to a wide variety of 5-ring heteroaromatics (Table 4). Electron rich arenes, such as pyrrole (**33**), indole (**47**), thiophene (**35**), benzothiophene (**49**), and benzofuran (**51**) gave the corresponding annulated products in good to excellent yields (entries 1–2, 9–11, Table 4). Annulated isoxazole **30** and thiazole **40** were obtained in good yields (entries 3 and 5, Table 4), whereas pyrazoles did not give any product (entries 7 and 8, Table 4), which is in line with the lack of previous cyclisation reports. On substrates with two potential radical addition sites this cyclisation was regioselective, as demonstrated by the formation of the annulated pyrrole (**34**), thiophene (**36**), and isoxazole (**30**) (entries 1–3, Table 4). We hypothesise this selectivity stems from the nature of the intermediary heterocyclic radical: reactions that proceed *via* intermediary allylic radicals occur, whereas ones lacking allylic conjugation do not (Scheme 3).^[57] The same argument can be invoked to explain the failed

Table 4. Heterocyclic reaction scope.

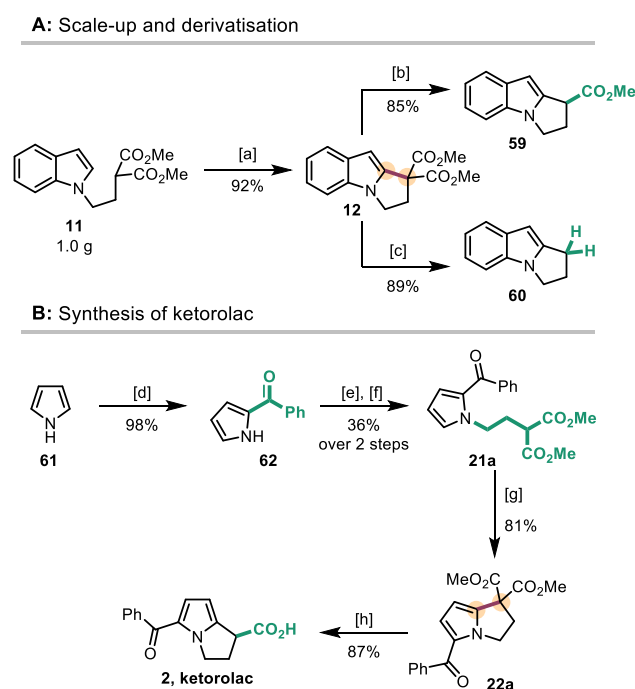
		
entry	substrate	product (isolated yield)
1		 34 (58%)
2		 36 (85%)
3		 30 (63%)
4		 38 (0%)
5		 40 (46%)
6		 42 (0%)
7		 44 (0%)
8		 46 (0%)
9		 48 (88%)
10		 50 (85%)
11		 52 (69%)
12		 54 (89%)
13		 56 (82%)
14		 58 (69%)

Reagents and conditions: substrate (0.20 mmol), NaHMDS (1.2 equiv.), NIS (1.2 equiv.), THF (0.1 M), –78 °C to RT, 5 h, then TMP (2.0 equiv.) 30 W white CFL, RT, 18 h.

cyclisation of isoxazole **37** and thiazole **41** (entries 4 and 6, Table 4). Finally, systems with basic nitrogens such as deazapurine **53**, azaindole **55**, and xanthine **57**^[58] cyclised to give the desired products in good yields (60–89%, entries 12–14, Table 4).

The malonate motif was not only useful as a reactive centre in the cyclisation but could be easily converted into the mono ester, as exemplified with indole **11** (Scheme 2A). This was achieved through Krapcho decarboxylation to give **59** and revealed a useful handle for further derivatisation. Extended reaction times yielded the fully decarboxylated product **60**, rendering the malonate a traceless linker.

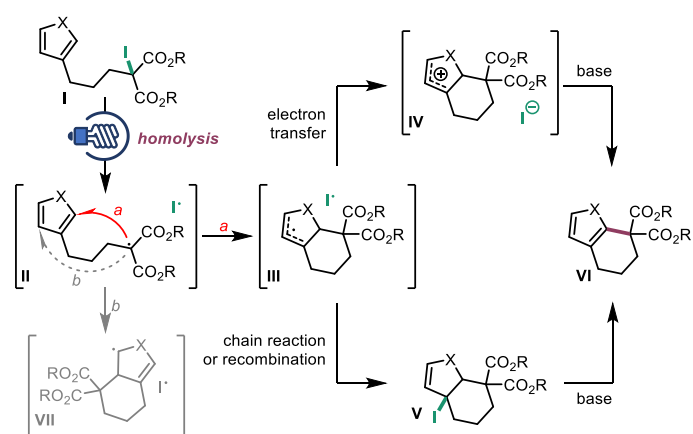
Finally, to further showcase the utility of this transformation we prepared the non-steroidal anti-inflammatory drug (NSAID) ketorolac (**2**), which was obtained from pyrrole **61** in 5 steps and 25% overall yield (Scheme 2B).



Scheme 2. Scale-up, derivatisations and synthesis of ketorolac. *Reagents and conditions:* (a) **11** (3.6 mmol), optimised cyclisation conditions (*vide supra*); (b) **12** (0.4 mmol), LiCl (5.0 equiv.), DMF (0.2 M), 150 °C, 2 h; (c) **12** (0.15 mmol), LiCl (10 equiv.), DMF (0.1 M), 150 °C, 17 h; (d) **61** (2.0 mmol), morpholino (phenyl)methanone (1.5 equiv.), POCl₃ (3.25 equiv.), CH₂Cl₂ (0.25 M), RT, 16 h; (e) **62** (2.5 mmol), 1,2-dibromoethane (20 equiv.), KOH (10 equiv.), DMSO (0.4 M), RT, 2 h; (f) dimethyl malonate (4.0 equiv.), K₂CO₃ (4.0 equiv.), DMF (0.15 M), 60 °C, 2 h; (g) **21a** (0.2 mmol), optimised cyclisation conditions (*vide supra*); (h) **22a** (0.12 mmol), aq. NaOH (1 M, 2.0 equiv.), MeOH (0.03 M), RT, 16 h, then aq. HCl (2 M).

Acylation of pyrrole **61** followed by *N*-alkylation and substitution provided malonate **21a**. Radical cyclisation gave pyrrole **22a** in good yield (81%), which upon decarboxylation provided ketorolac **2** (87%).^[55]

Regarding the mechanism of this reaction, we postulate that white light irradiation promotes the homolytic cleavage of the C–I bond in **I**, yielding the reactive malonyl radical **II** (Scheme 3).^[59] This then adds onto the vicinal heteroaromatic to form a stabilised allylic radical **III**, which can be converted into iodide **V** *via* abstraction of an iodine atom from a molecule of starting material, propagating a chain reaction, or *via* recombination with an iodine radical. Elimination of HI would then yield the desired product. Alternatively, this can also happen through an electron transfer within the caged radical pair to yield allyl cation **IV**, followed by elimination. This proposed mechanism is in line with the regiochemistry of the cyclisation of isoxazole **31**, pyrrole **33**, and thiophene **35**; and is supported by radical trapping experiments with TEMPO (entry 12, Table 1 and entry 13, Table 3. See Supporting Information, S18–19).



Scheme 3. Proposed mechanism for the light-mediated cyclisation of iodomalones.

Conclusion

In conclusion, we have developed a transition metal-free, visible light-mediated cyclisation of malonyl radicals onto a wide range of heteroaromatics under mild conditions. This methodology allows the synthesis of ring systems not previously reported and provides access to chemical space that may be of interest for drug design. The utility of this transformation was further demonstrated through the synthesis of the marketed drug ketorolac. Further work on the light-mediated cyclisation of malonates in complex systems is ongoing and will be reported in due course.

Experimental Section

General procedure for the synthesis of iodomalonates.

To a solution of the malonate (1.0 equiv.) in dry THF (5 mL/mmol of substrate) cooled to -78°C was added dropwise NaHMDS (1.0 M in THF, 1.2 equiv.) in the dark. The resulting solution was allowed to stir for 15 min at this temperature before the dropwise addition of *N*-iodosuccinimide (1.2 equiv.) in dry degassed THF (5 mL/mmol of substrate) over 5 min. The mixture was then allowed to stir at room temperature for 5 h in the dark. After this time, the reaction mixture was diluted with water (20 mL/mmol of substrate) and extracted with EtOAc (3×30 mL/mmol of substrate). The combined organic layers were dried over MgSO_4 and evaporated *in vacuo*. The crude mixture was purified by flash-chromatography.

General procedure for the one-pot cyclisation of malonates.

To a solution of the malonate (1.0 equiv.) in dry degassed THF (5 mL/mmol of substrate) cooled to -78°C was added dropwise NaHMDS (1.0 M in THF, 1.2 equiv.) in the dark. The resulting solution was allowed to stir for 15 min at this temperature before the dropwise addition of *N*-iodosuccinimide (1.2 equiv.) in dry degassed THF (5 mL/mmol of substrate) over 5 min. The mixture was then allowed to stir at room temperature for 5 h in the dark. After this time, TMP (2.0 equiv.) was added and the reaction mixture irradiated using a white 30 W CFL light (at 1.0 cm distance) for 16–24 h. After this time, all volatiles were removed *in vacuo* and the crude mixture purified by flash-chromatography.

Acknowledgements

PHL is grateful to the EPSRC Centre for Doctoral Training in Synthesis for Biology and Medicine (EP/L015838/1) for a studentship, generously supported by AstraZeneca, Diamond Light Source, Defence Science and Technology Laboratory, Evotec, GlaxoSmithKline, Janssen, Novartis, Pfizer, Syngenta, Takeda, UCB and Vertex and St John's College Oxford for funding. We thank Dr Simon Berritt (Pfizer) for optimisation of part of the substrate synthesis, and Dr Owen Smith for acquiring the X-ray crystallographic data for compound **58** (see Supporting Information).

References

- [1] For some discussion of ring systems in medicinal chemistry see: R. D. Taylor, M. MacCoss, A. D. Lawson, *J. Med. Chem.*, 2017, **60**, 1638-1647; R. Visini, J. Aruspous, M. Awale, J. L. Reymond, *J. Chem. Inf. Model.*, 2017, **57**, 2707-2718; R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845-5859.
- [2] M. Baumann, I. R. Baxendale, S. V. Ley, N. Nikbin, *Beilstein J. Org. Chem.* **2011**, **7**, 442-495.
- [3] M. Baumann, I. R. Baxendale, *Beilstein J. Org. Chem.* **2013**, **9**, 2265-2319.
- [4] Numerous indole alkaloids contain annulated heterocycles. For examples see: J. E. Saxton, *Nat. Prod. Rep.*, **1997**, **14**, 559-590; J. Leonard, *Nat. Prod. Rep.*, **1999**, **16**, 319-338.
- [5] K. Keck, *Z. Naturforschg.* **1968**, **23b**, 1034-1043.
- [6] K. N. V. Duong, A. Gaudemer, M. D. Johnson, R. Quillivic, J. Zylber, *Tetrahedron Lett.* **1975**, **16**, 2997-3000.
- [7] J. A. Murphy, M. S. Sherburn, *Tetrahedron Lett.* **1990**, **31**, 3495-3496.
- [8] J. A. Murphy, M. S. Sherburn, *Tetrahedron* **1991**, **47**, 4077-4088.
- [9] M. K. H. Doll, *J. Org. Chem.* **1999**, **64**, 1372-1374.
- [10] D. C. Harrowven, M. I. T. Nunn, *Tetrahedron Lett.* **1998**, **39**, 5875-5876.
- [11] F. E. Ziegler, L. O. Jeroncic, *J. Org. Chem.* **1991**, **56**, 3479-3486.
- [12] G. A. Kraus, H. Kim, *Synth. Commun.* **1993**, **23**, 55-64.
- [13] D. R. Artis, I.-S. Cho, S. Jaime-Figueroa, J. M. Muchowski, *J. Org. Chem.* **1994**, **59**, 2456-2466.
- [14] C.-P. Chuang, S.-F. Wang, *Synth. Commun.* **1994**, **24**, 1493-1505.
- [15] F. E. Ziegler, M. Belema, *J. Org. Chem.* **1994**, **59**, 7962-7967.
- [16] S. Ozaki, S. Mitoh, H. Ohmori, *Chem. Pharm. Bull.* **1996**, **44**, 2020-2024.
- [17] C. J. Moody, C. L. Norton, *J. Chem. Soc., Perkin Trans. I* **1997**, 2639-2644.
- [18] A. M. Rosa, A. M. Lobo, P. S. Branco, S. Prabhakar, A. M. D. L. Pereira, *Tetrahedron* **1997**, **53**, 269-284.
- [19] S.-F. Wang, C.-P. Chuang, *Tetrahedron Lett.* **1997**, **38**, 7597-7598.
- [20] F. E. Ziegler, M. Y. Berlin, *Tetrahedron Lett.* **1998**, **39**, 2455-2458.
- [21] L. D. Miranda, R. Cruz-Almanza, M. Pavón, E. Alva, J. M. Muchowski, *Tetrahedron Lett.* **1999**, **40**, 7153-7157.
- [22] S.-F. Wang, C.-P. Chuang, W.-H. Lee, *Tetrahedron* **1999**, **55**, 6109-6118.
- [23] D. R. Artis, I.-S. Cho, J. M. Muchowski, *Can. J. Chem.* **1992**, **70**, 1838-1842.
- [24] Y. Antonio, M. E. D. L. Cruz, E. Galeazzi, A. Guzman, B. L. Bray, R. Greenhouse, L. J. Kurz, D. A. Lustig, M. L. Maddox, J. M. Muchowski, *Can. J. Chem.* **1994**, **72**, 15-22.
- [25] K. Jones, T. C. T. Ho, J. Wilkinson, *Tetrahedron Lett.* **1995**, **36**, 6743-6744.
- [26] F. Aldabbagh, W. R. Bowman, E. Mann, *Tetrahedron Lett.* **1997**, **38**, 7937-7940.
- [27] T. C. T. Ho, K. Jones, *Tetrahedron* **1997**, **53**, 8287-8294.

- [28] F. Aldabbagh, W. R. Bowman, E. Mann, A. M. Z. Slawin, *Tetrahedron* **1999**, *55*, 8111-8128.
- [29] F. Aldabbagh, W. R. Bowman, *Tetrahedron Lett.* **1997**, *38*, 3793-3794.
- [30] J. Marco-Contelles, M. Rodríguez-Fernández, *Tetrahedron Lett.* **2000**, *41*, 381-384.
- [31] S. M. Allin, W. R. S. Barton, W. R. Bowman, T. McNally, *Tetrahedron Lett.* **2002**, *43*, 4191-4193.
- [32] M. Menes-Arzate, R. Martínez, R. Cruz-Almanza, J. M. Muchowski, Y. M. Osornio, L. D. Miranda, *J. Org. Chem.* **2004**, *69*, 4001-4004.
- [33] E. Paleo, Y. M. Osornio, L. D. Miranda, *Org. Biomol. Chem.* **2011**, *9*, 361-362.
- [34] T. Kaoudi, B. Quiclet-Sire, S. Seguin, S. Z. Zard, *Angew. Chem. Int. Ed.* **2000**, *39*, 731-733.
- [35] F. Gagosz, S. Z. Zard, *Org. Lett.* **2002**, *4*, 4345-4348.
- [36] J. W. Tucker, J. M. R. Narayanam, S. W. Krabbe, C. R. J. Stephenson, *Org. Lett.* **2010**, *12*, 368-371.
- [37] Itoh and co-workers have reported the cyclisation of malonates onto indoles to give annulated products in the presence of 20 mol% CaI_2 and light under air which can proceed *via* an iodomalonnate see: E. Yamaguchi, Y. Sudo, N. Tada, A. Itoh, *Adv. Synth. Catal.* **2016**, *358*, 3191-3195.
- [38] P. López-Mendoza, J. E. Díaz, A. E. Loaiza, L. D. Miranda, *Tetrahedron* **2018**, *74*, 5494-5502.
- [39] K. C. Forbes, A. M. Crooke, Y. Lee, M. Kawada, K. M. Shamskhov, R. A. Zhang, J. S. Cannon, *J. Org. Chem.* **2022**, *87*, 3498-3510.
- [40] M. Daniel, L. Fensterbank, J.-P. Goddard, C. Ollivier, *Org. Chem. Front.* **2014**, *1*, 551-555.
- [41] A. Citterio, R. Sebastiano, M. Caceres Carvayal, *J. Org. Chem.* **1991**, *56*, 5335-5341.
- [42] A. Citterio, R. Sebastiano, M. Nicolini, *Tetrahedron* **1993**, *49*, 7743-7760.
- [43] For examples of the use of malonyl radicals in heteroannulation reactions see: a) (indoles) ref 14; b) (indoles and pyrroles) ref 36; c) (indoles) ref. 37; d) (indoles and pyrroles) J. Magolan, M. A. Kerr, *Org. Lett.*, **2006**, *8*, 4561-4564; e) (indoles) J. E. C. Tejeda, B. K. Landschoot, M. A. Kerr, *Org. Lett.*, **2016**, *18*, 2142-2145; f) (indoles) C.-P. Chuang, S.-F. Wang, *Tetrahedron Lett.*, **1994**, *35*, 1283-1284; g) (indoles) A.-I. Tsai, C.-H. Lin, C.-P. Chuang, *Heterocycles*, **2005**, *65*, 2381-2394; h) (indoles) S.-F. Wang, C.-P. Chuang, *Heterocycles*, **1997**, *45*, 347-359.
- [44] D. A. Contreras-Cruz, M. Castañón-García, E. Becerril-Rodríguez, L. D. Miranda, *Synthesis* **2019**, *52*, 246-252.
- [45] E. Arceo, E. Montroni, P. Melchiorre, *Angew. Chem. Int. Ed. Engl.* **2014**, *53*, 12064-12068.
- [46] D. Fernandez Reina, A. Ruffoni, Y. S. S. Al-Faiyz, J. J. Douglas, N. S. Sheikh, D. Leonori, *ACS Catalysis* **2017**, *7*, 4126-4130.
- [47] D. P. Curran, M. H. Chen, E. Spletzer, C. M. Seong, C. T. Chang, *J. Am. Chem. Soc.* **1989**, *111*, 8872-8878.
- [48] E. Baciocchi, B. Giese, H. Farshchi, R. Ruzziconi, *J. Org. Chem.* **1990**, *55*, 5688-5691.
- [49] C.-B. Miao, Y.-H. Wang, M.-L. Xing, X.-W. Lu, X.-Q. Sun, H.-T. Yang, *J. Org. Chem.* **2013**, *78*, 11584-11589.
- [50] For reviews of manganese(III) acetate in organic synthesis see: a) B. B. Snider, *Chem. Rev.* **1996**, *96*, 339-363; b) G. G. Melikyan, *Org. React.* **1997**, *49*, 427-675; c) A. S. Demir, M. Emrullahoglu, *Curr. Org. Synth.* **2007**, *4*, 321-351; d) J. W. Burton (2012) in *Encyclopedia of Radicals in Chemistry, Biology and Materials*, C. Chatgililoglu, A. Studer (eds). John Wiley & Sons Ltd, Chichester, UK, pp 901-942; e) M. Mondal, U. Bora, *RSC Advances* **2013**, *3*, 18716-18754.
- [51] E. Baciocchi, D. Dell'Aira, R. Ruzziconi, *Tetrahedron Lett.* **1986**, *27*, 2763-2766.
- [52] There are a number of other methods for malonyl radical generation see for example: C. Wetter, K. Jantos, K. Woithe, A. Studer, *Org. Lett.*, **2003**, *5*, 2899-2902; S. R. Chowdhury, I. U. Hoque, S. Maity, *Chem. Asian. J.*, **2018**, *13*, 2824-2828; ref 41.
- [53] Radical additions/cyclisations onto imidazoles, thiazoles and pyrazoles that do not involve malonyl radicals are known. For examples see: refs 26, 28, 29, 31 and 57.
- [54] For photochemical atom-transfer addition reactions of iodomalonnates to alkenes and alkynes using 10 mol% hexabutylditin see: ref 47.
- [55] For a previous synthesis of ketolorac involving a key malonyl radical cyclisation see: ref 23.
- [56] Cyclopropane **6** may result from amide enolate displacement of the iodomalonnate formed in situ from malonnate **4**.
- [57] D. A. Nagib, D. W. C. MacMillan, *Nature* **2011**, *480*, 224-228.
- [58] The structure of **58**, and hence of **57**, was confirmed by X-ray crystallography of **58**. CCDC-2097518 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [59] See Supporting Information for UV/VIS studies including spectra of iodomalonnate **29** and its mixtures with TMP, succinimide, and HMDS. Although electron donor-acceptor (EDA) complexes can be necessary for photochemical reactions to proceed we did not find evidence for formation on an EDA complex in our system. For recent reviews on EDA complexes in organic photochemistry see: a) G. E. M. Crisenza, D. Mazzarella, P. Melchiorre, *J. Am. Chem. Soc.* **2020**, *142*,

5461-5476; b) Z. Yang, Y. Liu, K. Cao, X. Zhang, H. Jiang, J. Li, Beilstein J. Org. Chem. 2021, 17, 771-799.

RESEARCH ARTICLE

Transition Metal-Free, Visible Light-Mediated Radical Cyclisation of Malonyl Radicals onto 5-Ring Heteroaromatics

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Pol Hernández-Lladó, Kilian Garrec, Daniel C. Schmitt, Jonathan W. Burton*

