Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2022, **20**, 8209

Received 12th September 2022,
Accepted 11th October 2022

DOI: 10.1039/d2ob01663j

rsc.li/obc

Aza-[4 + 2] cycloadditions employing catalytically derived *N*-acyliminium ions†

Niamh J. Owen and Mark G. McLaughlin *

Herein, we report the development of a novel route to tricyclic lactam products *via* a facile aza-[4 + 2] cycloaddition of catalytically generated acyliminium ions. Employing a $Ca(NTf_2)_2$/nBu_4NPF_6 catalyst system in low loadings, a range of diverse fused ring systems can be synthesised in predominantly good yields.

The development of new methods to access small, fused ring systems bearing multiple functional groups and synthetic handles remains an important goal within synthetic organic chemistry. 3-Substitued isoindolones represent an important pharmacophore found in an increasing number of bioactive small molecules,[1,2] with growing interest in tertiary substituted aza-cycles (Fig. 1).

Access to these fragments is typically through intramolecular cyclisation of pendant sp-rich functional groups,[3] mediated by both stoichiometric[4,5] and catalytic Lewis acids (Fig. 2).[6] Further cyclisation reactions employing stoichiometric Brønsted acids have also been reported.[7,8] Additional methods include aza-Navarov cyclisation cascades[9] and tandem Aza-Prins/Friedel–Crafts reactions.[10] Although these methods present elegant solutions, many of them take advantage of the inherent reactivity of a pendant functional group. This somewhat limits the scope of the reaction and builds in additional synthetic steps. Herein, we report our work in developing a [4 + 2] cycloaddition protocol to produce 6,5,6 fused tertiary aza-cycles in good to excellent yields.

Our work began by taking advantage of our previously reported methodology to access *N*-acyliminium ions *via* catalytic dehydration.[11–14] We therefore began our investigation using these conditions, employing hydroxyisoindolinone **1** and dimethylbutadiene (**2a**) as model substrates (Table 1). As shown, optimisation of temperature, solvent, and catalyst loading led to conditions that afforded the [4 + 2] product in high isolated yield. In essence, the reaction proceeded in a range of solvents, with temperature being the variable that had the biggest impact. Furthermore, running the reaction in the absence of any part of the catalyst system was unsuccessful.

With these conditions now optimised, we wanted to explore the substrate tolerance of the reaction, with particular emphasis on differing electronics. As shown (Fig. 3), *para*-electron donating (**3b**) and withdrawing (**3c**) groups afforded the

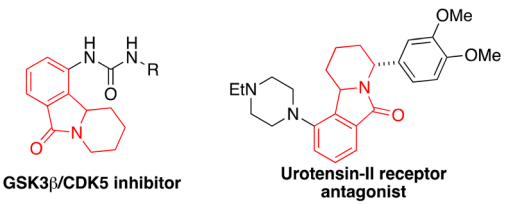


Fig. 1 Exemplar bioactive small molecules.

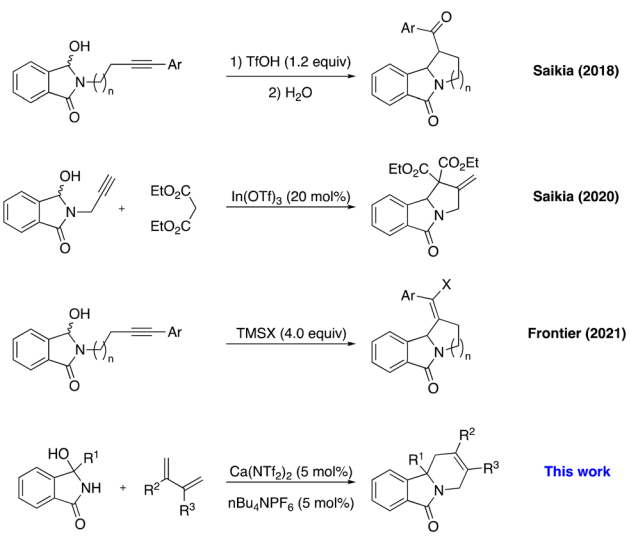
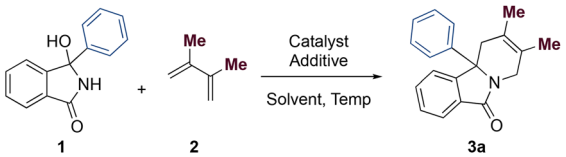


Fig. 2 Recent methods to access isoindolone cores.

Department of Chemistry, Lancaster University, Bailrigg, LA14YB, UK.
E-mail: m.mclaughlin3@lancaster.ac.uk

† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d2ob01663j

Table 1 Optimisation studies



Entry	Catalyst	Additive	Loading	Temp.	Solvent	Time (min)	Yield
1	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	65 °C	DCM	30	73%
2	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	65 °C	EtOAc	30	81%
3	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	65 °C	DCE	30	82%
4	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	65 °C	HFIP	30	57%
5	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	65 °C	Toluene	30	71%
6	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	40 °C	DCE	30	n.r.
7	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	50 °C	HFIP	60	57%
8	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	80 °C	EtOAc	90	70%
9	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	80 °C	DCE	90	82%
10	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	80 °C	Toluene	90	76%
11	$Ca(NTf_2)_2$	nBu_4NPF_6	5 mol%	80 °C	DCE	60	82%
12	**$Ca(NTf_2)_2$**	**nBu_4NPF_6**	**5 mol%**	**80 °C**	**DCE**	**30**	**88%**[a]
13	$Ca(NTf_2)_2$	nBu_4NPF_6	1 mol%	80 °C	DCE	90	32%
14	$Ca(NTf_2)_2$	nBu_4NPF_6	1 mol%	80 °C	DCE	120	74%[a]
15	$Ca(NTf_2)_2$	—	5 mol%	80 °C	DCE	30	n.r.
16	—	nBu_4NPF_6	5 mol%	80 °C	DCE	30	n.r.
17	—	—	—	80 °C	DCE	30	n.r.

[a] 1.5 equiv. diene used.

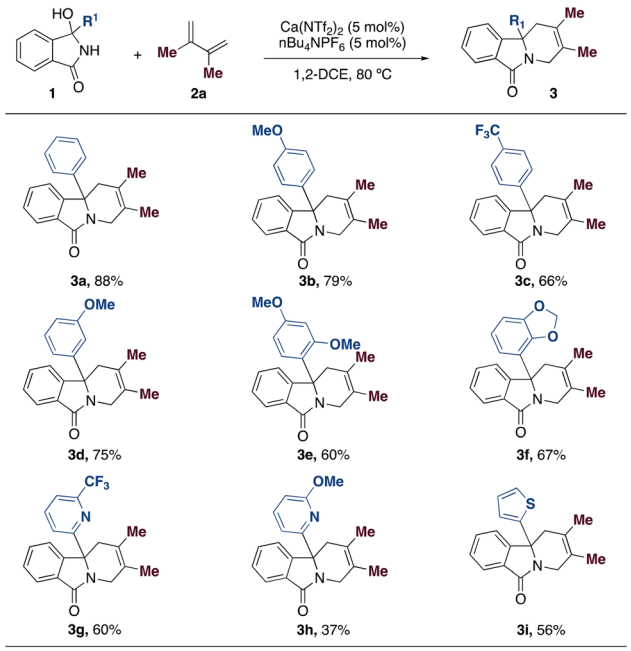


Fig. 3 Dimethyl butadiene derived products.

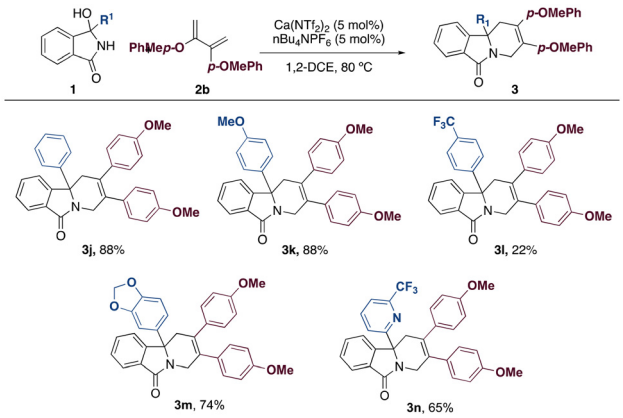


Fig. 4 Further substrate scope.

desired product in good yield, with a small reduction in yield observed in the trifluoromethyl substrate. *meta*-Electron withdrawing (**3d**) and *ortho, para*- (**3e**) electron donating groups both worked well, as did benzodioxole (**3f**). Heterocycles were also tolerated, with pyridyl (**3g**, **3h**) and thiazole (**3i**) derivatives being synthesised in moderate yields.

We also explored bis-phenyl diene **2b**, which was also well tolerated in most cases (Fig. 4). The trifluromethyl group (**3l**) retarded the reaction, with prolonged reaction times and higher temperatures having little effect on the overall conversion.

We next turned our attention to unsymmetrical dienes, as up to this point, we have employed dienes bearing the same group at each position. To this end, diene **4** was synthesised[15] and subjected to the above optimised conditions (Fig. 5).

Once again, the reaction was tolerant to a variety of different functional groups including electron donating (**5b**) and withdrawing groups (**5c**, **5d**), *meta* (**5e**) and acid sensitive (**5f**) functionalities. Furthermore, sulfur (**5g**) and nitrogen (**5h**, **5i**) containing heterocycles provided the desired products in

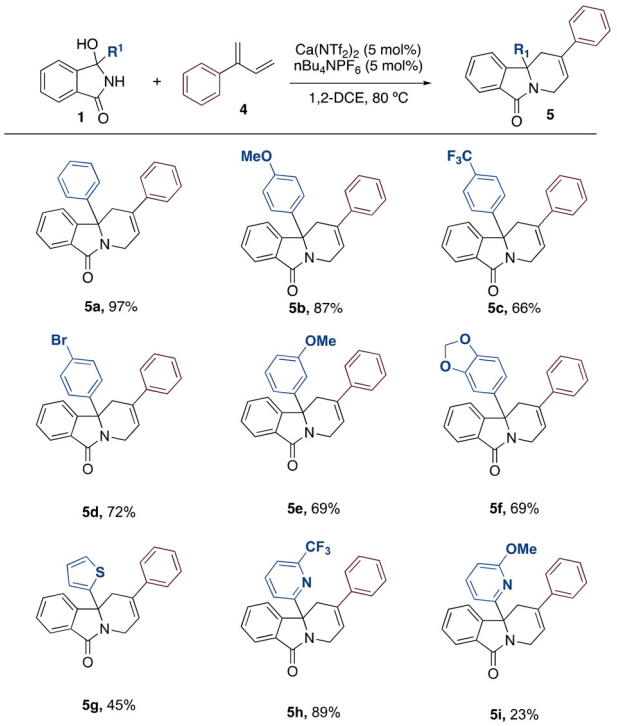


Fig. 5 Unsymmetrical diene substrate scope.

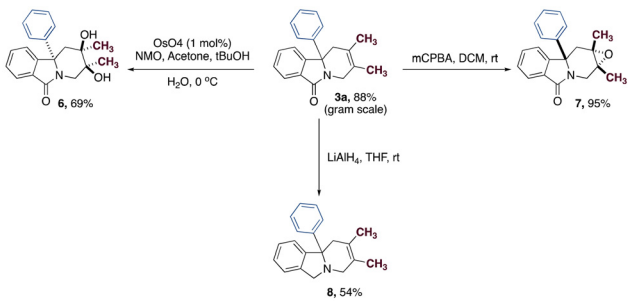


Fig. 6 Synthetic manipulation of synthesised fragments.

decent to good yields. In all cases, only a single isomer was observed and isolated, with no evidence of other isomers present, as determined by ^{1}H-NMR of the crude reaction mixture.

Finally, we wanted to explore the synthetic utility of these compounds (Fig. 6). To this end, **3a** was synthesised on gram scale in excellent yield. Subjecting **3a** to Upjohn dihydroxylation conditions (OsO_4 (cat), NMO) provided diol **6**, as a single diastereomer in good yield, while Prilezhaev epoxidation (*m*CPBA) gave epoxide **7**, once again as single diastereomer in excellent yield. Finally, lithium aluminium hydride reduction afforded the pyridoisoindole **8** in decent yield.

Conclusions

In conclusion, we have described the development of a novel aza-[4 + 2] cycloaddition reaction employing catalytically derived *N*-acyliminium ions. This reaction is tolerant to a wide range of functional groups and allows for the synthesis of diverse fused fragments from readily accessible hydroxyisoindolinones and dienes. Furthermore, the synthetic utility of the products has been demonstrated.

Conflicts of interest

There are no conflicts to declare.

References

1 D. K. Luci, E. C. Lawson, S. Ghosh, W. A. Kinney, C. E. Smith, J. Qi, Y. Wang, L. K. Minor and B. E. Maryanoff, *Tetrahedron Lett.*, 2009, **50**, 4958–4961.
2 T. Honma, T. Yoshizumi, N. Hashimoto, K. Hayashi, N. Kawanishi, K. Fukasawa, T. Takaki, C. Ikeura, M. Ikuta, I. Suzuki-Takahashi, T. Hayama, S. Nishimura and H. Morishima, *J. Med. Chem.*, 2001, **44**, 4628–4640.
3 Y. Quevedo-Acosta, I. D. Jurberg and D. Gamba-Sánchez, *Eur. J. Org. Chem.*, 2022, e202200432.
4 J. J. Hernandez and A. J. Frontier, *Org. Lett.*, 2021, **23**, 1782–1786.
5 X.-Y. Liu, X.-M. Luo and L.-F. Tang, *Tetrahedron*, 2020, **76**, 131341.
6 A. K. Sahu, R. Unnava, S. Shit and A. K. Saikia, *J. Org. Chem.*, 2020, **85**, 1961–1971.
7 A. K. Saikia, K. Indukuri and J. Das, *Org. Biomol. Chem.*, 2014, **12**, 7026–7035.
8 M. Das and A. K. Saikia, *J. Org. Chem.*, 2018, **83**, 6178–6185.
9 K. K. S. Sai, M. J. O'Connor and D. A. Klumpp, *Tetrahedron Lett.*, 2011, **52**, 2195–2198.
10 K. Indukuri, R. Unnava, M. J. Deka and A. K. Saikia, *J. Org. Chem.*, 2013, **78**, 10629–10641.
11 A. J. Basson, N. R. Halcovitch and M. G. McLaughlin, *Chem. – Eur. J.*, 2022, e202201107.
12 A. J. Basson and M. G. McLaughlin, *J. Org. Chem.*, 2020, **85**, 5615–5628.
13 A. J. Basson and M. G. McLaughlin, *ChemSusChem*, 2021, **14**, 1696–1699.
14 A. J. Basson and M. G. McLaughlin, *Chem. Commun.*, 2019, **55**, 8317–8320.
15 D. Fiorito, S. Folliet, Y. Liu and C. Mazet, *ACS Catal.*, 2018, **8**, 1392–1398.