

# One-pot cross-metathesis/tandem carbonyl ylide formation–intramolecular cycloaddition of an unsaturated 2-diazo-3,6-diketoester

David M. Hodgson,\* Deepshikha Angrish and Agnès H. Labande†

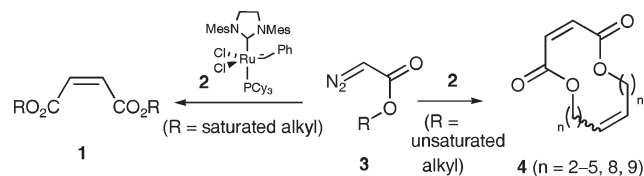
Received (in Cambridge, UK) 10th November 2005, Accepted 11th January 2006

First published as an Advance Article on the web 18th January 2006

DOI: 10.1039/b515943a

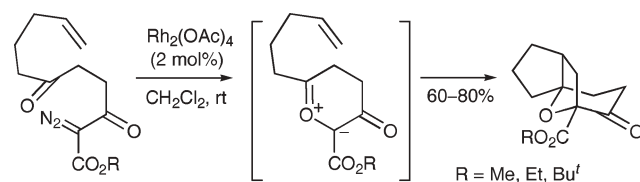
Dicarbonyl-stabilised diazo functionality is tolerated during alkene cross-metathesis using Grubbs' catalyst, but undergoes subsequent tandem carbonyl ylide formation–intramolecular 1,3-dipolar cycloaddition on addition of catalytic  $\text{Rh}_2(\text{OAc})_4$  in a one-pot operation.

We recently reported that Grubbs' 2nd-generation ruthenium carbene catalyst **2** induces stereoselective homocoupling (dimerisation) of  $\alpha$ -diazoacetates **3** to maleates **1**.<sup>1</sup> Metathetical activity was retained in the presence of additional alkene functionality, which allows one-pot homocoupling/ring-closing metathesis to give dienyldilactones **4** (Scheme 1).



Scheme 1

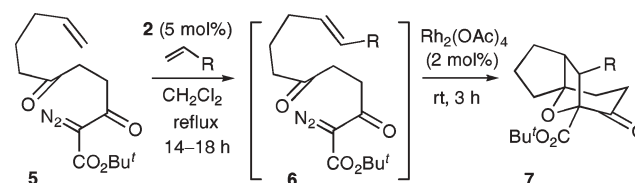
On exploring the tolerance of differently substituted  $\alpha$ -diazo compounds to metathesis catalysts, we found that the diazo derivative of ethyl acetoacetate (ethyl 2-diazo-3-oxobutanoate) was stable to catalyst **2**. This suggested that alkene metathesis might proceed in the presence of such (more substituted) diazo functionality. If viable, this would provide a way to rapidly diversify unsaturated diazo compounds (for example, by alkene cross-metathesis).<sup>2</sup> The retained diazo functionality could then be used to facilitate a range of (different) transition metal-catalysed carbene transfer reactions (e.g. cyclopropanation, C–H insertion, ylide chemistry),<sup>3</sup> typically involving the newly elaborated olefin.



Scheme 2

Transition metal-catalysed tandem carbonyl ylide formation–1,3-dipolar cycloadditions of  $\alpha$ -diazo carbonyl compounds constitute powerful methodology for the concise synthesis of oxapolycycles<sup>4</sup> (e.g. Scheme 2).<sup>5</sup> In the present paper, we communicate the viability of directly coupling this latter process with chemoselective alkene cross-metathesis of an unsaturated diazo compound.

The ability to carry out cross-metathesis in the presence of dicarbonyl-stabilised diazo functionality was first studied. Thus, cross-metathesis of unsaturated 2-diazo-3,6-diketoester **5**<sup>5a</sup> with various monosubstituted olefins (2–10 equiv.) was examined using catalyst **2** (5 mol%) in  $\text{CH}_2\text{Cl}_2$  at reflux for 14–18 h (Scheme 3, Table 1). Pleasingly, cross-metathesis proceeded smoothly in good yields and with high control of stereoselectivity for most of the 1,2-disubstituted olefins **6**. Styrene and substituted styrenes generally underwent efficient cross-metathesis (entries 3, 4, 6–9). However, 4-methoxystyrene was a reluctant partner in the process (entry 5); even with a large excess (10–15 equiv.) the reaction failed to reach completion after 48 h at reflux.



Scheme 3

Table 1 Cross-metathesis and cycloaddition using ester **5**

Entry	R	<b>6</b> Yield % (E : Z)	<b>7</b> Yield (%)	Yield over 2-steps (%)	Yield One-pot (%)
1	CO <sub>2</sub> Me	74 (E-only)	89	66	69
2	Cy	78 (85 : 15)	78	61	63
3	Ph	81 (E-only)	84	68	73
4	4-MeC <sub>6</sub> H <sub>4</sub>	69 (94 : 6)	86	59	77
5	4-MeOC <sub>6</sub> H <sub>4</sub>	46 (E-only) <sup>a</sup>	quant.	46	43
6	4-ClC <sub>6</sub> H <sub>4</sub>	76 (E-only)	82	62	68
7	4-FC <sub>6</sub> H <sub>4</sub>	76 (96 : 4)	87	66	75
8	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	79 (E-only)	quant.	79	76
9	2-ClC <sub>6</sub> H <sub>4</sub>	89 (96 : 4)	78	69	80

<sup>a</sup> 74% based on recovered **5**.

The disubstituted olefins **6** underwent efficient tandem carbonyl ylide formation–intramolecular cycloaddition catalysed by  $\text{Rh}_2(\text{OAc})_4$  (2 mol%) in  $\text{CH}_2\text{Cl}_2$  at rt for 3–4 h to give cycloadducts **7** (78%–quant. yields). These results expand the range of substituted alkene dipolarophiles that can be used in this (intramolecular) cycloaddition chemistry.<sup>6</sup>

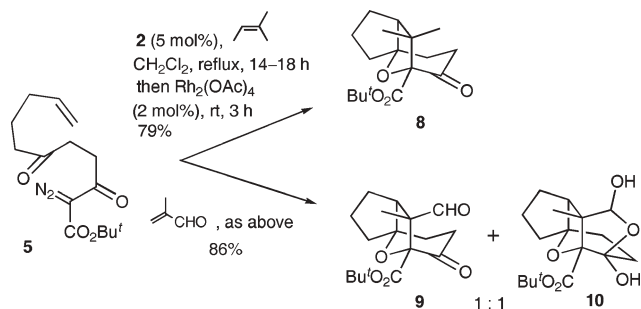
Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, UK OX1 3TA.

E-mail: david.hodgson@chem.ox.ac.uk

† Present address: Laboratoire de Chimie de Coordination – CNRS UPR 8241, 205 route de Narbonne, 31077 Toulouse, Cedex 4, France. E-mail: labande@lcc-toulouse.fr

We also studied one-pot cross-metathesis/intramolecular carbonyl ylide cycloaddition reactions, to see if the spent Ru catalyst following metathesis would affect the subsequent Rh(II)-catalysed cycloaddition.<sup>7</sup> The one-pot cross-metathesis/carbonyl ylide cycloadditions were carried out using catalyst **2** (5 mol%) in CH<sub>2</sub>Cl<sub>2</sub> at reflux for 14–18 h, followed by addition of Rh<sub>2</sub>(OAc)<sub>4</sub> (2 mol%) after cooling to rt.† This sequential process proceeded smoothly to yield the desired cycloadducts **7** in good to excellent yields, compared to the yields over 2 steps (Table 1).  $\alpha,\beta$ -Unsaturated ester intermediate **6** (R = CO<sub>2</sub>Me) yielded the desired cycloadduct **7** (R = CO<sub>2</sub>Me) in good yield in one-pot. No competing intermolecular 1,3-dipolar cycloaddition<sup>8</sup> was observed with the excess of unreacted methyl acrylate present from the cross-metathesis reaction (entry 1).

We also examined the one-pot strategy with trisubstituted olefins generated by cross-metathesis of  $\alpha$ -diazo- $\beta$ -ketoester **5** with amylene and methacrolein (Scheme 4). The cross-metathesis reactions proceeded smoothly to generate the corresponding trisubstituted olefins [*t*-butyl 2-diazo-11-methyl-3,6-dioxododec-10-enoate and (*E*)-*t*-butyl 2-diazo-11-methyl-3,6,12-trioxododec-10-enoate] in good yields (77% and 83%, respectively). Subsequent carbonyl ylide cycloadditions gave the cycloadducts **8** and **9/10** in 74% and 77% yield, respectively. The cycloadduct **9** from methacrolein was isolated as a 1 : 1 mixture with its cyclic hydrate **10**.<sup>9</sup> The one-pot protocol yielded the cycloadducts **8** and **9/10** in higher yield (79% from amylene and 86% from methacrolein) than the combined yield over the two individual steps (cross-metathesis and cycloaddition), 57% and 64% respectively.



Scheme 4

In summary, Grubbs' 2nd generation ruthenium carbene complex **2** undergoes stereoselective cross-metathesis in the presence of diazo functionality (when the latter is flanked by two carbonyl groups). The spent ruthenium catalyst allows added Rh<sub>2</sub>(OAc)<sub>4</sub> to catalyse carbonyl ylide cycloadditions, thus establishing the compatibility of these two late transition metal complexes sequentially catalysing different carbene transfer reactions. The scope of one-pot metathesis followed by other

transformations of pre-existing diazo functionality is under investigation.

We thank the University of Oxford for a full Clarendon Fund bursary award (to D. A.), the European Union for a Marie Curie Fellowship (HPMF-CT-2000-00559 to A. H. L.) and the EPSRC National Mass Spectrometry Service Centre for mass spectra.

## Notes and references

† Typical procedure for one-pot cross-metathesis/cycloaddition: Grubbs' 2nd-generation catalyst **2** (21 mg, 0.025 mmol) was added to a solution of 2-diazo-3,6-diketoester **5**<sup>5a</sup> (147 mg, 0.50 mmol) and styrene (0.23 cm<sup>3</sup>, 2.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 cm<sup>3</sup>) and the reaction mixture was heated to reflux for 14 h. After cooling to rt, Rh<sub>2</sub>(OAc)<sub>4</sub> (5 mg, 0.01 mmol) was added and the reaction mixture was stirred at room temperature for 3 h. The mixture was then concentrated under reduced pressure and purified by flash chromatography (SiO<sub>2</sub>, 30% Et<sub>2</sub>O in petrol) to afford a pale yellow oil, cycloadduct **7** (R = Ph) (125 mg, 73%); R<sub>f</sub> = 0.41 (50% Et<sub>2</sub>O in petrol);  $\nu_{\text{max}}$ (neat)/cm<sup>-1</sup> 3421br, 3019s, 2959s, 2872s, 2400s, 2253s, 1734s, 1458s, 1370w, 1217s and 1158w;  $\delta_{\text{H}}$ (400 MHz; CDCl<sub>3</sub>) 7.32–7.20 (5H, m, Ph), 3.40 (1H, d, J 8, CHPh), 2.88–2.68 (2H, m, CHCH<sub>2</sub> and CH of CH<sub>2</sub>), 2.62–2.48 (2H, m, CH<sub>2</sub>), 2.17 (1H, dd, J 6 and 8, CH of CH<sub>2</sub>), 2.12–1.82 (3H, m, CH<sub>2</sub> and CH of CH<sub>2</sub>), 1.82–1.50 (2H, m, CH<sub>2</sub>), 1.58–1.44 (1H, m, CH of CH<sub>2</sub>) and 1.46 (9H, s, CMe<sub>3</sub>);  $\delta_{\text{C}}$ (100 MHz; CDCl<sub>3</sub>) 203.7 (CO), 166.2 (CO<sub>2</sub>), 137.4 (*ipso*), 128.6, 128.1 and 126.9 (3 × Ar), 93.5 and 91.8 (COC, quat.), 82.6 (CMe<sub>3</sub>), 60.5 (CHPh), 53.9 (CHCH<sub>2</sub>), 37.2, 36.2, 33.5, 33.1 and 24.5 (5 × CH<sub>2</sub>) and 27.8 (CMe<sub>3</sub>); *m/z* (CI) 360 (M + NH<sub>4</sub><sup>+</sup>, 62%) and 304 (100); Found M + NH<sub>4</sub> 360.2167. C<sub>21</sub>H<sub>30</sub>O<sub>4</sub>N requires *M* 360.2169.

- D. M. Hodgson and D. Angrish, *Chem. Commun.*, 2005, 4902–4904.
- (a) *Handbook of Metathesis*, ed. R. H. Grubbs, Wiley-VCH, Weinheim, 2003; (b) A. K. Chatterjee, T.-L. Choi, D. P. Sanders and R. H. Grubbs, *J. Am. Chem. Soc.*, 2003, **125**, 11360–11370.
- M. P. Doyle, M. A. McKervey and T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, John Wiley and Sons, New York, 1998.
- (a) M. P. Doyle, M. A. McKervey and T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, John Wiley and Sons, New York, 1998, pp. 289–354; (b) M. C. McMills and D. Wright, in *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, eds. A. Padwa and W. H. Pearson, John Wiley and Sons, New York, 2002, vol. 59, pp. 253–314; (c) *Nitrogen, Oxygen and Sulfur Ylide Chemistry*, ed. J. S. Clark, Oxford University Press, Oxford, 2002; (d) G. Mehta and S. Muthusamy, *Tetrahedron*, 2002, **58**, 9477–9504; (e) D. A. Selden and D. M. Hodgson, in *Comprehensive Organic Functional Group Transformations II*, ed. K. Jones, Elsevier, Oxford, 2004, vol. 3, pp. 309–353.
- (a) D. M. Hodgson, P. A. Stuppel, F. Y. T. M. Pierard, A. H. Labande and C. Johnstone, *Chem.-Eur. J.*, 2001, **7**, 4465–4476; (b) See also: D. M. Hodgson, T. Brückl, R. Glen, A. H. Labande, D. A. Selden, A. G. Dossetter and A. J. Redgrave, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 5450–5454.
- D. M. Hodgson, A. H. Labande, F. Y. T. M. Pierard and M. Á. Expósito Castro, *J. Org. Chem.*, 2003, **68**, 6153–6159.
- For other one-pot processes involving alkene cross-metathesis, see: (a) S. D. Goldberg and R. H. Grubbs, *Angew. Chem., Int. Ed.*, 2002, **41**, 807–810; (b) B. M. Trost, J. L. Gunzner, O. Dirat and Y. H. Rhee, *J. Am. Chem. Soc.*, 2002, **124**, 10396–10415; (c) J. Cossy, F. Bargiggia and S. BouzBouz, *Org. Lett.*, 2003, **5**, 459–462.
- A. Padwa, S. F. Hornbuckle, G. E. Fryxell and Z. J. Zhang, *J. Org. Chem.*, 1992, **57**, 5747–5757.
- For a related observation, see: D. M. Hodgson, F. Le Strat, T. D. Avery, A. C. Donohue and T. Brückl, *J. Org. Chem.*, 2004, **69**, 8796–8803.