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A novel route to substituted 4-methylene-4,5-dihydroisoxazoles mediated by hafnium(IV) chloride

Peter J. Dunn,^a Alison B. Graham,^b Ronald Grigg,^{*b} Paul Higginson,^a Visuvanthar Sridharan and Mark Thornton-Pett^b

^a Pfizer Global Research & Development (UK), Sandwich, Kent, UK CT13 9NJ

^b Molecular Innovation, Diversity and Automated Synthesis (MIDAS) Centre, School of Chemistry, The University of Leeds, Leeds, UK LS2 9JT. E-mail: R.Grigg@chem.leeds.ac.uk

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Heating alkyl vinyl ketones and N-tert-butylarylmethylideneamine N-oxides in the presence of HfCl₄ results in the formation of 4-methylene-4,5-dihydroisoxazoles in good vield.

We recently reported that hafnium(IV) chloride is an excellent catalyst for the tandem 1,3-azaprotio cyclotransfer-cycloaddition reaction between aldoximes and divinyl ketone, inducing the formation of the exo-isomers of substituted 1-aza-8-oxabicyclo[3.2.1]octan-4-ones 3 and reversing the natural regioselectivity of the thermally promoted cascade (Scheme 1).¹ We proposed that the dramatic effect on regioselectivity was due to coordination of the Lewis acid to the carbonyl moiety of the intermediate nitrone enhancing nucleophilicity at the β carbon and promoting the formation of 3.



To study the effect of HfCl₄ on a similar intermolecular 1,3-dipolar cycloaddition we reacted N-tert-benzylideneamine N-oxide 5a with methyl vinyl ketone 6a. Under thermal conditions (MeCN, reflux, 48 h) a 4:1 mixture of 5-substituted isoxazolidines exo-7 and endo-7 was obtained in 34% combined yield (Scheme 2). When the same substrates were subjected to the HfCl₄ catalysed conditions outlined in Scheme 1 only starting material was obtained after the usual reaction time of 30 min. Increasing the reaction time to 8 h did not result in the formation of the expected 4-substituted isoxazolidine 9

0 MeCN `*t*-Bu t-Bu reflux HfCl₄ (0.5 eq.) 5a 48h THF, reflux, 8h (34%) 0 (51%)D٢ H₃COC сн∍ exo-7 8a CH t-Bu 6a COCH₃ 9

Scheme 2



but, instead, furnished 4-methylene-4,5-dihydroisoxazole 8a (80% conversion of nitrone, 51% yield). The structure of 8a was determined by X-ray crystallography (Fig. 1).† Anhydrous $Sc(OTf)_3$ also induced the formation of **8a** (0.5 eq. $Sc(OTf)_3$, THF, reflux, 8 h) in slightly lower yield (80% nitrone conversion, 48% yield) whereas the addition of ZnBr₂ (0.5 eq.) under otherwise identical reaction conditions did not induce the formation of 8a (1H NMR indicated that the crude reaction mixture was comprised of starting material and traces of the products of a 1,3-dipolar cycloaddition).



Fig. 1 X-Ray crystal structure of 8a.†

Further development of this process identified conditions that afford reproducible results (Scheme 3).² The methodology encompasses both electron-donating and electron-withdrawing groups on the aromatic ring and variation of the ketone component (6a-c) (Table 1). In addition to 8a-h, which were obtained as single stereoisomers, traces (5%) of the corresponding aromatic aldehydes (from degradation of 5a-f, vide infra) were visible in the ¹H NMR spectra of crude products. The stereochemistry of the double bond in compounds 8b-h was assigned by correlation of the chemical shift and coupling constants of the C=CH and CH2 moieties in the 1H NMR spectra with those obtained for 8a.



Scheme 3

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 Table 1 Hafnium(IV) chloride mediated synthesis of 4-methylene-4,5-dihydroisoxazoles

Nitrone		Vii	ıyl ket	one			Produ	ict ^a	Yie	ld ^b	(%)
5a		6a					8a		75		
5b		6a					8b		76		
5c		6a					8c		68		
5d		6a					8d		54		
5e		6a					8e		64		
5f		6a					8f		70		
5a		6b					8g		64		
5a		6c					8ĥ		31		
<i>a</i> In all	cases	apart	from	5a	+	6a,	small	amounts	(5-10%)	of	the

corresponding aldehydes were detected by ¹H NMR. ^{*b*} Yield isolated by flash chromatography.

The mechanism of the reaction is a matter of conjecture at present. HfCl₄ catalysed degradation of nitrone **5a** may generate benzaldehyde and a hafnium complexed hydroxylamine if traces of water are present in the system. Indeed small amounts of the corresponding aromatic aldehydes are visible in the ¹H NMR spectra of the crude products and the amount of these was found to be proportional to the quantity of catalyst and reaction time. The hydroxylamine may react with **6a** to generate nitrone **10**³ followed by a 6 π -electrocyclisation–aldol condensation–dehydration sequence to generate **8a** (Scheme 4). Analogous 6 π -electrocyclisation reactions are well known.^{4–6}



Scheme 4

In summary, we report a novel route to 4-methylene-4,5-dihydroisoxazoles from readily available starting materials.⁷ The synthetic value of these systems, and conventional methods to generate them are the subject of a recent review by Zecchi *et al.*⁸ Further studies of the mechanism and scope of the reaction are in progress.

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Notes and references

† *Crystal data*. C₁₁H₁₁NO, *M* = 173.21, orthorhombic, *Pcba*, *a* = 12.3331(2), *b* = 7.3853(2), *c* = 20.0230(9) Å, *U* = 1823.77(10) Å³, *Z* = 8, Mo-Kα radiation, λ = 0.71073 Å, *m* = 0.081 mm⁻¹, *T* = 150(2) K, *R*₁ = 0.0449 for 1319 reflections with *I* > 2σ(*I*), *wR*₂ = 0.1063 for all 1787 independent data. CCDC 168614. See http://www.rsc.org/suppdata/cc/b1/ b105561p/ for crystallographic data in .cif or other format. Methods and programmes were standard from the SHELX suite.⁹

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- 2 Typical experimental procedure: methyl vinyl ketone **6a** (0.75 mmol) was added to a solution of nitrone **5a** (0.5 mmol) and HfCl₄ (0.75 mmol) in dry THF (20 mL) under a nitrogen atmosphere and the resulting homogeneous solution stirred at reflux for 24 h. The reaction mixture was quenched by the addition of saturated NaHCO₃ solution and extracted with dichloromethane. The combined organic extracts were washed with water, dried (MgSO₄), filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography, eluting with 1:1 v/v diethyl ether–pentane to afford the product **8a** as a colourless crystalline solid (0.065 g, 75%). Recrystallisation from dichloromethane–pentane afforded the product as colourless needles, mp 107.5–109 °C.
- 3 When the corresponding oxime of **6a** and benzaldehyde were heated under the reaction conditions (HfCl₄ (0.5 eq.), THF, reflux, 8 h) no traces of **8a** were detected and only unreacted material was recovered.
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