ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Synthesis of 3,3-disubstituted indoline-2-thiones catalysed by an N-heterocyclic carbene†

Cite this: *Chem. Commun.*, 2014, **50**, 8871

Received 27th May 2014,
Accepted 15th June 2014

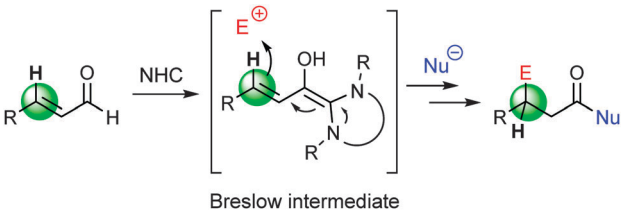
DOI: 10.1039/c4cc04047c

www.rsc.org/chemcomm

Hideo Ikota, Takayuki Ishida, Chihiro Tsukano and Yoshiji Takemoto*

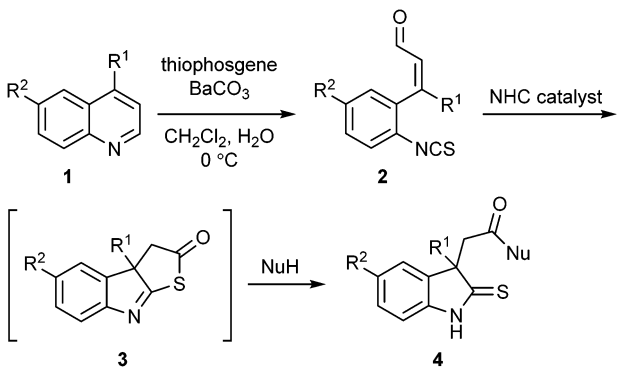
A catalytic method has been developed for construction of indoline-2-thiones containing an all-carbon quaternary centre at the C-3 position. Successive treatment of α,β-unsaturated aldehydes bearing an isothiocyanato moiety with an *in situ* generated N-heterocyclic carbene and an appropriate heteroatomic nucleophile provided the 3,3-disubstituted indoline derivatives in moderate to good yields.

Umpolung strategies involving the use of N-heterocyclic carbenes (NHC)[1] have attracted considerable attention in the field of organic synthesis since Breslow[2] proposed a mechanism for the benzoin condensation reaction in 1958 involving the use of a thiazolium salt. Following this initial publication, a variety of other NHC-catalysed reactions have been reported, including a Stetter reaction,[3] as well as reactions involving enolate generation,[4] and redox acylation.[5] Homoenolate equivalents, which can be readily prepared by the reaction of the corresponding α,β-unsaturated aldehydes with an NHC catalyst, are well known to be unique umpolung synthons that possess a nucleophilic β-carbon unit (Scheme 1). The first synthetic applications of homoenolate equivalents, in terms of their reaction with electrophilic species, were reported independently by Bode[6a] and Glorius[6b,c] in 2004, and a large number of related reactions have subsequently been developed.[7–10] Reports pertaining to the reaction of β,β-disubstituted enals, however, have been limited in number and only a few reactions have been explored, including the asymmetric protonation of homoenolates, which was reported by Scheidt[11] and Ma's synthesis of butenolide from β-chloroenal.[12] Given that neither of these reactions leads to the formation of an all-carbon quaternary centre, there still remains an urgent need for the development of synthetic methods capable of providing access to all-carbon quaternary centres from β,β-disubstituted enals.



Scheme 1 Umpolung of enals by an NHC catalyst.

Indoline and its congeners represent the core structures of a large number of natural products and biologically active compounds,[13] and extensive research efforts have consequently been directed towards the development of efficient synthetic methods for the construction of these substructures.[14] With this in mind, it was envisaged that an NHC-catalysed process could be developed for the synthesis of indoline-2-thione **4** from β,β-disubstituted α,β-unsaturated aldehydes **2** bearing an isothiocyanato moiety,[15] which could be readily derived from quinolines **1** according to the method reported by Hull[16] (Scheme 2). If the NHC catalyst reacted predominantly with the formyl group of enal **2** instead of the isothiocyanato moiety, then the resulting Breslow intermediate would undergo successive C–C and S–C bond forming reactions with the isothiocyanato moiety to give the desired 2*H*-thienoindolones **3**



Scheme 2 Synthesis of 3,3-disubstituted indoline-2-thiones.

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan. E-mail: takemoto@pharm.kyoto-u.ac.jp; Fax: +81-075-753-4569; Tel: +81-075-753-4528

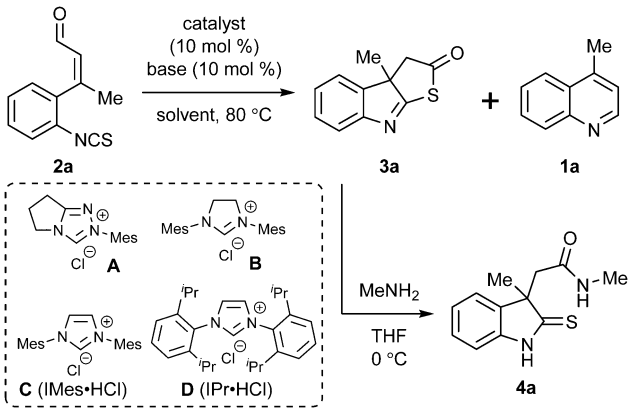
† Electronic supplementary information (ESI) available. CCDC 992277. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc04047c

together with the generation of an all-carbon quaternary centre at the C-3 position. Herein, we report the concise synthesis of 3,3-disubstituted indoline-2-thiones **4** from enal **2** *via* a tandem NHC-catalysed five-membered thiolactam formation/nucleophilic ring opening reaction.

We initially examined the NHC-catalysed cyclisation of enal **2a**[17] with several different NHC precursors **A–D** (Table 1). The reactions were carried out in the presence of 10 mol% of each NHC precursor and potassium *tert*-butoxide in toluene at 80 °C. The reactions involving the use of triazolium salt **A** and imidazolinium salt **B** led to the generation of quinoline **1a** and the *E*/*Z* isomerisation of substrate **2a**, but did not afford any of the desired product **3a** (Table 1, entries 1 and 2). However, imidazolium salts **C** (IMes·HCl) and **D** (IPr·HCl) promoted the desired reaction to give 2*H*-thienoindolone **3a** as the major product (Table 1, entries 3 and 4). Since **3a** was not stable to silica gels, the purification of the reaction mixture by column chromatography resulted in a poor isolated yield (16%), and the product ratios of **3a**/**1a**/**2a** reported in Table 1 were consequently evaluated by the ^{1}H NMR analysis of the crude mixtures. The yield of **3a** could be estimated from the isolated yield of indoline-2-thione **4a**, which was obtained by the subsequent addition of an appropriate nucleophile to the reaction mixture. Indeed, the tandem NHC-catalyzed cyclization and ring-opening reaction of **2a** and methylamine in the presence of **D** provided the corresponding amide **4a** in 75% yield, and the structure of **4a** was unambiguously determined by X-ray crystallographic analysis.[18] We then proceeded to investigate the effect of different bases on the outcome of the reaction (Table 1, entries 5–7). Although potassium or caesium carbonate furnished the desired product **3a**, DBU was totally ineffective in this reaction. In any event, potassium *tert*-butoxide was superior to all of the other bases examined in this study in terms of the chemical yield. Interestingly, the subsequent screening of solvents revealed that this reaction proceeded only in aromatic hydrocarbon solvents such as toluene and benzene (Table 1, entries 8–11).

Under these optimised conditions, the scope and limitations of this reaction were investigated with respect to both the nucleophiles (NuH) used for the ring-opening reaction and the substituents (R^1 and R^2) of the enals **2** (Table 2). As for the ring opening of intermediate **3a**, various nucleophiles such as aniline, methanol, and thiophenol could be used in the tandem reaction, with the corresponding amide **4b**, ester **4c**, and thioester **4d** products being formed in reasonable yields, respectively (Table 2, entries 2–4). This reaction was also applicable to the synthesis of Weinreb amide **4e** by the reaction of **3a** with a mixture of *N*,*O*-dimethylhydroxylamine hydrochloride and triethylamine (Table 2, entry 5). Along with the methyl group, various primary alkyl groups were also well tolerated as R^1 substituents, including ethyl, homobenzyl and homoallyl groups, which gave the

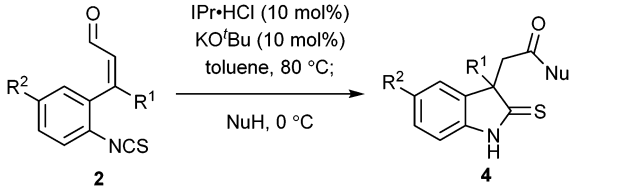
Table 1 Optimization of conditions

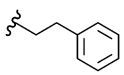
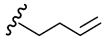
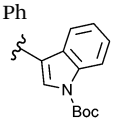


Entry	Catalyst	Base	Solvent	**3a** : **1a** : **2a**[a,b]	Yield of **4a**[c] (%)
1	**A**	KO^{t}Bu	Toluene	0 : 21 : 79	—
2	**B**	KO^{t}Bu	Toluene	0 : 6 : 94	—
3	**C**	KO^{t}Bu	Toluene	50 : 10 : 40	—
4	**D**	KO^{t}Bu	Toluene	90 : 5 : 5	75
5	**D**	K_2CO_3	Toluene	50 : 14 : 36	—
6	**D**	Cs_2CO_3	Toluene	80 : 15 : 5	—
7	**D**	DBU	Toluene	0 : 20 : 80	—
8	**D**	KO^{t}Bu	THF	0 : 42 : 58	—
9	**D**	KO^{t}Bu	1,2-DCE	0 : 0 : 100	—
10	**D**	KO^{t}Bu	DMF	0 : 63 : 37	—
11	**D**	KO^{t}Bu	Benzene	84 : 12 : 4	72

[a] Product ratios (**3a** : **1a** : **2a**) were determined by ^{1}H NMR analysis of crude materials. [b] Recovered **2a** contained an *E*-isomer. [c] Isolated yield.

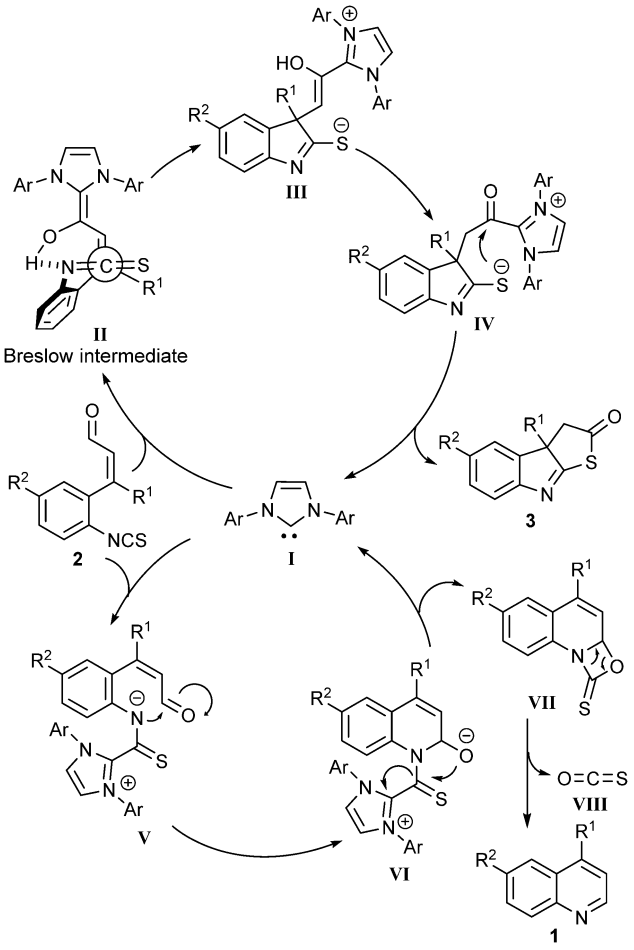
Table 2 Scopes and limitations



Entry	Substrate	NuH	R^1	R^2	Product	Yield[a] (%)
1	**2a**	$MeNH_2$	Me	H	**4a**	75
2[b,c]	**2a**	$PhNH_2$	Me	H	**4b**	62
3[b,c]	**2a**	MeOH	Me	H	**4c**	59
4[c]	**2a**	PhSH	Me	H	**4d**	48
5[c,d]	**2a**	Me(MeO)NH	Me	H	**4e**	50
6	**2f**	$MeNH_2$	Et	H	**4f**	66
7	**2g**	$MeNH_2$		H	**4g**	67
8	**2h**	$MeNH_2$		H	**4h**	78
9	**2i**	$MeNH_2$	^{i}Pr	H	**4i**	68
10[e]	**2j**	$MeNH_2$	^{t}Bu	H	**4j**	35
11	**2k**	$MeNH_2$	Ph	H	**4k**	89
12	**2l**	$MeNH_2$		H	**4l**	60
13	**2m**	$MeNH_2$	Me	Me	**4m**	73
14	**2n**	$MeNH_2$	Me	OMe	**4n**	75
15	**2o**	$MeNH_2$	Me	NMe_2	**4o**	44
16	**2p**	$MeNH_2$	Me	Cl	**4p**	43
17	**2q**	$MeNH_2$	Me	Br	**4q**	55

[a] Isolated yield. [b] Addition of NuH was carried out with 1.0 equivalent of *N*,*N*-dimethyl-4-aminopyridine. [c] Addition of NuH was carried out at room temperature. [d] Addition of NuH was carried out with Me(MeO)NH·HCl and Et_3N. [e] The reaction was performed at 100 °C.

corresponding products **4f–h** in 66, 67, and 78% yields, respectively (Table 2, entries 6–8). Although the same reaction of **2i** bearing an isopropyl group afforded the desired product **4i** in 68% yield (Table 2, entry 9), the *tert*-butyl derivative **2j** underwent the cyclisation quite slowly at 80 °C, and it was necessary to increase the reaction temperature to 100 °C to obtain thioamide **4j** bearing two contiguous quaternary carbon centres, albeit in 35% yield (Table 2, entry 10). The β-arylated enals **2k** and **2l** were also applicable to the tandem reaction, and reacted smoothly and without any difficulty to give the corresponding products **4k** and **4l** in 89 and 60% yields, respectively (Table 2, entries 11 and 12). Notably, the latter adduct included two indole motifs, bearing different oxidation states. The effect of the R^2 substituent on the aromatic ring was also examined, and substrates **2m** and **2n** bearing electron-donating groups (Me and MeO), on their aromatic ring reacted smoothly under the optimised conditions to give the corresponding products **4m** and **4n** in 73% and 75% yields, respectively (Table 2, entries 13 and 14). In contrast, enals **2o–q** bearing either a dimethylamino moiety or a halogen atom proved to be poor substrates for the tandem reaction because of their poor solubility or low reactivity. As a result, only moderate yields of the desired products **4o**, **4p**, and **4q** were observed, which were accompanied by the recovery of the starting materials (Table 2, entries 15–17).



Scheme 3 Proposed reaction mechanism.

The proposed mechanism of the NHC-catalysed reaction using catalyst **D** is shown in Scheme 3. The reaction would be initiated by the formation of Breslow intermediate **II**, which would be formed from enal **2** and the *in situ* generated NHC **I**. Since intermediate **II** could be regarded as a homoenolate equivalent, the intramolecular C–C bond forming reaction between the β-carbon of the enal and the isothiocyanate carbon would proceed to give the enol intermediate **III**. It was assumed that the transition state for the C–C bond-forming reaction would be stabilised by a hydrogen-bonding interaction between the aldehyde-derived hydroxyl moiety and the isothiocyanato moiety of intermediate **II** in a similar manner to that reported by Scheidt.[4d,7d] Following the tautomerisation from enol **III** to acylazolium salt **IV**, the nucleophilic substitution of the NHC by the sulphur atom of the thioimidate anion would provide the 2*H*-thienoindolone **3** together with the regeneration of catalyst **I**. The formation of quinoline **1** as a major by-product would be triggered by the nucleophilic addition of either a base or the NHC catalyst to the isothiocyanato moiety of **2**, which would be followed by the intramolecular condensation of the resulting nitrogen anion with an aldehyde (**V** → **VI** → **VII**).

In conclusion, we have developed a novel tandem NHC-catalysed 2*H*-thienoindolone formation and nucleophilic ring-opening reaction involving α,β-unsaturated aldehydes bearing an isothiocyanato moiety. This reaction allows for the concise synthesis of various 3,3-disubstituted indoline-2-thiones containing all-carbon quaternary centres at the C-3 position in moderate to good yields.

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

Notes and references

1 For selected reviews, see: (*a*) D. Enders and T. Balensiefer, *Acc. Chem. Res.*, 2004, **37**, 534; (*b*) K. Zeitler, *Angew. Chem., Int. Ed.*, 2005, **44**, 7506; (*c*) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5606; (*d*) N. Marion, S. Díez-González and S. P. Nolan, *Angew. Chem., Int. Ed.*, 2007, **46**, 2988; (*e*) V. Nair, S. Vellalath and B. P. Babu, *Chem. Soc. Rev.*, 2008, **37**, 2691; (*f*) V. Nair, R. S. Menon, A. T. Biju, C. R. Sinu, R. R. Paul, A. Jose and S. Vellalath, *Chem. Soc. Rev.*, 2011, **40**, 5336; (*g*) X. Bugaut and F. Glorius, *Chem. Soc. Rev.*, 2012, **41**, 3511; (*h*) X.-Y. Chen and S. Ye, *Org. Biomol. Chem.*, 2013, **11**, 7991; (*i*) S. J. Ryan, L. Candish and D. W. Lupton, *Chem. Soc. Rev.*, 2013, **42**, 4906.

2 (*a*) R. Breslow, *J. Am. Chem. Soc.*, 1958, **80**, 3719; (*b*) R. Breslow and E. McNeils, *J. Am. Chem. Soc.*, 1960, **82**, 2394.

3 For selected examples of NHC-catalysed Stetter reactions, see: (*a*) H. Stetter and H. Kuhlmann, *Chem. Ber.*, 1976, **109**, 2890; (*b*) E. Ciganek, *Synthesis*, 1995, 1311; (*c*) D. Enders, K. Breuer, J. Runsink and J. H. Teles, *Helv. Chim. Acta*, 1996, **79**, 1899; (*d*) M. S. Kerr, J. R. de Alaniz and T. Rovis, *J. Am. Chem. Soc.*, 2002, **124**, 10298; (*e*) J. Zhang, C. Xing, B. Tiwari and Y. R. Chi, *J. Am. Chem. Soc.*, 2013, **135**, 8113.

4 For selected examples of NHC-catalysed enolate reactions, see: (*a*) M. He, J. R. Struble and J. W. Bode, *J. Am. Chem. Soc.*, 2006, **128**, 8418; (*b*) J. Kaeobamrung, M. C. Kozlowski and J. W. Bode, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 20661; (*c*) X. Fang, X. Chen and Y. R. Chi, *Org. Lett.*, 2011, **13**, 4708; (*d*) E. O. McCusker and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2013, **52**, 13616.

5 For the first examples of NHC-catalysed internal redox reactions, see: (*a*) K. Y.-K. Chow and J. W. Bode, *J. Am. Chem. Soc.*, 2004, **126**, 8126; (*b*) N. T. Reynolds, J. R. de Alaniz and T. Rovis, *J. Am. Chem. Soc.*, 2004, **126**, 9518For selected reviews, see: (*c*) H. U. Vora,

P. Wheeler and T. Rovis, *Adv. Synth. Catal.*, 2012, **354**, 1617; (*d*) J. Mahatthananchai and J. W. Bode, *Acc. Chem. Res.*, 2014, **47**, 696.

6 (*a*) S. S. Sohn, E. L. Rosen and J. W. Bode, *J. Am. Chem. Soc.*, 2004, **126**, 14370; (*b*) C. Burstein and F. Glorius, *Angew. Chem., Int. Ed.*, 2004, **43**, 6205; (*c*) C. Burstein, S. Tschan, X. Xie and F. Glorius, *Synthesis*, 2006, 2418.

7 For selected studies on [3+2] annulations, see: (*a*) M. He and J. W. Bode, *Org. Lett.*, 2005, **7**, 3131; (*b*) V. Nair, S. Vellalath, M. Poonoth, R. Mohan and E. Suresh, *Org. Lett.*, 2006, **8**, 507; (*c*) A. Chan and K. A. Scheidt, *J. Am. Chem. Soc.*, 2008, **130**, 2740; (*d*) K. P. Jang, G. E. Hutson, R. C. Johnston, E. O. McCusker, P. H.-Y. Cheong and K. A. Scheidt, *J. Am. Chem. Soc.*, 2014, **136**, 76.

8 For selected studies on cyclopentenation reactions, see: (*a*) V. Nair, S. Vellalath, M. Poonoth and E. Suresh, *J. Am. Chem. Soc.*, 2006, **128**, 8736; (*b*) V. Nair, B. P. Babu, S. Vellalath and E. Suresh, *Chem. Commun.*, 2008, 747; (*c*) B. Cardinal-David, D. E. A. Raup and K. A. Scheidt, *J. Am. Chem. Soc.*, 2010, **132**, 5345; (*d*) W. W. Y. Leong, X. Chen and Y. R. Chi, *Green Chem.*, 2013, **15**, 1505.

9 For examples of NHC-catalysed intramolecular β-nucleophilic addition of enals, see: (*a*) J. R. Struble and J. W. Bode, *Tetrahedron*, 2009, **65**, 4957; (*b*) C. R. Sinu, D. V. M. Padmaja, U. P. Ranjini, K. C. S. Lakshmi, E. Suresh and V. Nair, *Org. Lett.*, 2013, **15**, 68.

10 For selected studies on addition to nitroolefins, see: (*a*) V. Nair, C. R. Sinu, B. P. Babu, V. Varghese, A. Jose and E. Suresh, *Org. Lett.*, 2009, **11**, 5570; (*b*) B. Maji, L. Ji, S. Wang, S. Vedachalam, R. Ganguly and X.-W. Liu, *Angew. Chem., Int. Ed.*, 2012, **51**, 8276; (*c*) N. A. White, D. A. DiRocco and T. Rovis, *J. Am. Chem. Soc.*, 2013, **135**, 8504.

11 (*a*) B. E. Maki, A. Chan and K. A. Scheidt, *Synthesis*, 2008, 1306; (*b*) B. E. Maki, E. V. Patterson, C. J. Cramer and K. A. Scheidt, *Org. Lett.*, 2009, **11**, 3942.

12 (*a*) Y. Wu, W. Yao, L. Pan, Y. Zhang and C. Ma, *Org. Lett.*, 2010, **12**, 640; (*b*) W. Yao, M. Bian, G. Wang and C. Ma, *Synthesis*, 2011, 1998.

13 For selected reviews on natural products containing indole and related skeletons, see: (*a*) J. S. Bindra, in *The Alkaloids*, ed. R. H. F. Manske, Academic Press, New York, 1973, vol. 14, pp. 84–121; (*b*) M. Ishikura and K. Yamada, *Nat. Prod. Rep.*, 2009, **26**, 803; (*c*) A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev.*, 2010, **110**, 4489.

14 For reviews, see: (*a*) A. B. Dounay and L. E. Overman, *Chem. Rev.*, 2003, **103**, 2945; (*b*) H. Lin and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2003, **42**, 36; (*c*) C. Marti and E. M. Carreira, *Eur. J. Org. Chem.*, 2003, 2209; (*d*) A. Steven and L. E. Overman, *Angew. Chem., Int. Ed.*, 2007, **46**, 5488; (*e*) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748; (*f*) B. M. Trost and M. K. Brennan, *Synthesis*, 2009, 3003; (*g*) F. Zhou, Y.-L. Liu and J. Zhou, *Adv. Synth. Catal.*, 2010, **352**, 1381; (*h*) R. Dalpozzo, G. Bartoli and G. Bencivenni, *Chem. Soc. Rev.*, 2012, **41**, 7247; (*i*) N. R. Ball-Jones, J. J. Badillo and A. K. Franz, *Org. Biomol. Chem.*, 2012, **10**, 5165.

15 For examples of NHC-catalysed reactions of ketene and nitroalkene with isothiocyanate, see: (*a*) C. Awasthi and L. D. S. Yadav, *Synlett*, 2010, 1783; (*b*) X.-N. Wang, L.-T. Shen and S. Ye, *Org. Lett.*, 2011, **13**, 6382.

16 (*a*) R. Hull, *J. Chem. Soc. C*, 1968, 1777; (*b*) R. Hull, P. J. van den Broek and M. L. Swain, *J. Chem. Soc., Perkin Trans. 1*, 1975, 922.

17 The stereochemistry of starting material **2a** was confirmed as (*Z*)-configuration by using 2D NMR experiments including NOESY.

18 CCDC 992277.

