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## COMMUNICATION

## Kulinkovich-type reactions of thioamides: similar to those of carboxylic amides?<sup>†</sup>

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The behaviour of thioamides under Kulinkovich-type conditions is compared with the known reactivity of carboxylic amides. Dramatic differences are disclosed.

Since the original report by the group of Kulinkovich in 1989,<sup>1</sup> the transformations mediated by excess amounts of Grignard reagents in the presence of alkoxytitanium(IV) species of the type XTi(OiPr)<sub>3</sub> (X = Cl, OiPr) have emerged as a family of powerful reactions with remarkably broad scope.<sup>2</sup> In particular, the Kulinkovich–de Meijere cyclopropanation of carboxylic amides can now be considered as the method of choice for the synthesis of tertiary cyclopropylamines.<sup>2,3,4</sup> The alkene ligand-exchange version of this process is especially interesting, as it allows the inter- or intra-molecular coupling of a carboxylic amide and an olefin (Scheme 1).

The mechanism involves the formation of a titanacyclopropane **A** resulting from the reaction of the Grignard reagent with the



Scheme 1 Kulinkovich-de Meijere reaction with ligand exchange.

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Scheme 2 Comparison of the reactivities of amide **1aO** and thioamide **1aS** under Kulinkovich-type conditions.

starting titanium(iv) reagent. After ligand exchange with the olefin partner, a new titanacyclopropane complex **B** is generated, which then undergoes 1,2-insertion of the carbonyl group to afford an oxatitanacyclopentane intermediate **C**. The following elementary steps eventually deliver the aminocyclopropane product. The reaction has been shown to be diastereospecific with respect to the configuration of the alkene.<sup>5,6</sup> In this context, we wondered how thioamides would behave, under Kulinkovich-type conditions, as compared with carboxylic amides. This communication is an account of our preliminary results.

At first glance, the differences between the reactions of the *N*-alkenylamide **1aO** and the corresponding thioamide **1aS** under standard conditions could be judged as minor. The main product is the aminocyclopropane **2a** resulting from an intramolecular Kulinkovich–de Meijere reaction (Scheme 2). Besides this transformation, the thioamide **1aS** is also partly converted into the cyclopentyl-substituted tertiary amine **3a** or the cyclohexyl derivative **4a** depending on the Grignard reagent used, namely cyclopentylmagnesium chloride or cyclohexylmagnesium chloride.

In contrast, the reactions of **1bO/1bS** and the reactions of **1cO/1cS** in the presence of styrene are clearly divergent: these amides and the corresponding thioamides exhibit completely orthogonal behaviours (Scheme 3). In fact, while the carboxylic amide **1bO** undergoes an intramolecular Kulinkovich–de Meijere reaction to give the original 2-azabicyclo[5.1.0]octane **2b**,<sup>7</sup> no trace of this compound is observed starting from the thioacetamide **1bS** 

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Scheme 3 Amides vs. thioamides: examples of divergent reactions. *Conditions*:  $Ti(OiPr)_4$  (1.5 equiv.),  $cC_6H_{11}MgCl$  (4.0 equiv.), THF, 0 to 20 °C.

and only the cyclohexane-substituted tertiary amine **4b** is formed, with moderate conversion. The reaction of the formamide **1cO** and styrene to form **2c** had already been described by de Meijere *et al.* under slightly different conditions.<sup>6</sup> Our result is closely similar and no reductive alkylation product **4c** is formed. Conversely, using the thioamide **1cS** in place of **1cO**, **4c** is obtained in 65% yield and **2c** is not observed.

These examples convincingly suggest that the initially formed titanacyclopropane **A** reacts much faster with thioamide functions than with alkene groups. This is in sharp contrast with the known reactivity of carboxylic amide and ester groups, which have been demonstrated to be less reactive than terminal alkene functions towards the intermediates involved in Kulinkovich-type reactions.<sup>8</sup>

As a logical consequence, we expected that the observed reductive alkylation process could be generally performed in the absence of an olefin reactant. The results, obtained from several non-alkene thioamide substrates and presented in Table 1, confirmed this hypothesis. In all cases, the expected alkylated products 3-5 were obtained, generally in moderate yields. The effect of the choice of the solvent was briefly examined: while both tBuOMe and THF are suitable, cyclohexane performs less well (entry 7) and, perhaps unsurprisingly, dichloromethane is not compatible with the transformation (entry 13). The three Grignard reagents employed, namely isopropyl-, cyclopentyl- and cyclohexyl-magnesium chloride give comparable yields. It is worthy of note that the thiolactams 1fS and 1gS perform significantly better than the acyclic thioamides. The chiral substrate 1gS is converted into the corresponding amines 4g and 5g with some diastereoselectivity (entries 10–12). Interestingly, when the reaction of 1cS and cyclohexylmagnesium chloride was quenched with D<sub>2</sub>O, 92% deuterium incorporation was evidenced on the tertiary amine product 4c, at the position shown (entry 4).<sup>9</sup>

To explain the observed results, we propose a mechanism whereby the starting thioamide 1 would react with the primary titanacyclopropane intermediate A to give a thiatitanacyclopropane species D by a ligand exchange process (Scheme 4).



<sup>*a*</sup> Reaction conditions: Ti(O*i*Pr)<sub>4</sub> (1.5 equiv.), RMgCl (4.0 equiv.), in the solvent indicated, at 20 °C or 0 to 20 °C, typically for 60 min. <sup>*b*</sup> The yields and, if relevant, the diastereoisomeric ratios (dr) have been evaluated by NMR analysis of the crude products. The yields in parentheses are given for the isolated products. <sup>*c*</sup> The reaction was quenched with D<sub>2</sub>O. <sup>*d*</sup> Deuterium incorporation  $\approx 92\%$ . <sup>*e*</sup> The *cis* diastereoisomer was obtained predominantly.

An equilibrium of the complex **D** with the metallated iminium species **E** can then be invoked. Trapping of **E** by the Grignard reagent would afford the  $\alpha$ -metallated amine **F**. Upon hydrolysis or deuteriolysis, this ultimate intermediate of the reaction would then be transformed into the products **3–5**. From the substrate



Scheme 4 Proposed mechanism for the titanium-mediated transformation of thioamides 1 into tertiary amines 3–5.

**1aS**, it is reasonable to invoke a competitive pathway giving the bicyclic intermediate **CaS** by an intramolecular 1,2-insertion of the terminal alkene side-chain into the metallacycle **D**. The tentative titanium complex **CaS** would eventually afford **2a** in the same way as from the analogous sulfur-free species **C** (Scheme 1). In the cases of the reaction of **1bS** or the reaction of **1cS** with styrene, this alternative pathway is expected to be much slower because it would involve the formation of a seven-membered ring or an intermolecular process.

To account for the rather modest yields obtained, one can invoke a competitive direct addition of the Grignard reagent onto the starting thioamide. Indeed, the main by-product generally observed is the secondary amine **6** (produced in up to 37% yield). Cyclohexylmethylketone is detected by NMR in the crude products of the reactions carried out with cyclohexylmagnesium chloride starting from the thioaceamide **1dS** and **1eS**. However, the rather minor amounts of this ketone (8–15% yield) suggest that **6** could also be formed by another mechanism, possibly by an elimination elementary step, somewhere in a pathway following the formation of **D**. In the case of the thiolactam reactants **1fS** and **1gS**, such a process could be reversible, hence the better results obtained with these compounds.

In summary, thioamides behave drastically differently from carboxylic amides under Kulinkovich-type conditions. A metallative alkylation reaction is observed, with an important competitive pathway being the production of a secondary amine. The transformation is thought to operate *via* a thia-titanacyclopropane intermediate that can be trapped intramolecularly by an olefin group placed at a suitable distance. We are currently carrying out further investigations to get deeper insight into the reaction mechanism, improve its efficiency and develop novel extensions. Our results will be reported in due course.

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## Notes and references

- G. Kulinkovich, S. V. Sviridov, D. A. Vasilevskii and T. S. Prityskaya, *Zh. Org. Khim.*, 1989, 25, 2244–2245 (*Russ. J. Org. Chem.*, 1989, 25, 2027–2028).
- 2 Recent reviews: (a) J. K. Cha and O. G. Kulinkovich, in Organic Reactions, ed. S. E. Denmark, John Wiley & Sons, 2012, vol. 77, ch. 1; (b) A. Wolan and Y. Six, *Tetrahedron*, 2010, **66**, 15–61; (c) A. Wolan and Y. Six, *Tetrahedron*, 2010, **66**, 3097–3133.
- 3 Initial report: V. Chaplinski and A. de Meijere, Angew. Chem., 1996, 108, 491–492 (Angew. Chem., Int. Ed. Engl., 1996, 35, 413–414).
- 4 Dedicated review: A. de Meijere, S. I. Kozhushkov and A. I. Savchenko, J. Organomet. Chem., 2004, 689, 2033–2055; see also: A. de Meijere, V. Chaplinski, H. Winsel, M. Kordes, B. Stecker, V. Gazizova, A. I. Savchenko, R. Boese and F. Schill (née Brackmann), Chem.-Eur. J., 2010, 16, 13862–13875.
- 5 (a) C. P. Casey and N. A. Strotman, J. Am. Chem. Soc., 2004, 126, 1699–1704; (b) N. Ouhamou and Y. Six, Org. Biomol. Chem., 2003, 1, 3007–3009.
- 6 Examples involving disubstituted alkenes are few, because the formation of the intermediate **B** is less favoured than in the case of monosubstituted alkenes. See A. de Meijere, C. M. Williams, A. Kourdioukov, S. V. Sviridov, V. Chaplinski, M. Kordes, A. I. Savchenko, C. Stratmann and M. Noltemeyer, *Chem.–Eur. J.*, 2002, **8**, 3789–3801.
- Very few compounds with this skeleton have been described. Selected references: (a) L. Jerome, T. D. Sheppard, A. E. Aliev and W. B. Motherwell, *Tetrahedron Lett.*, 2009, **50**, 3709–3712; (b) Á. Mallagaray, G. Domínguez, A. Gradillas and J. Pérez-Castells, *Org. Lett.*, 2008, **10**, 597–600; (c) Y. S. Park and P. Beak, *Tetrahedron*, 1996, **52**, 12333–12350.
- 8 Selected references: (a) O. G. Kulinkovich, A. I. Savchenko, S. V. Sviridov and D. A. Vasilevski, *Mendeleev Commun.*, 1993, 230–231; (b) J. Lee, H. Kim and J. K. Cha, J. Am. Chem. Soc., 1996, **118**, 4198–4199.
- 9 Attempted trapping of the final intermediate with benzaldehyde was unsuccessful: the simple reductive alkylation product **4c** was obtained.