Author/s:
Hutton, CA;Shang, J;Wille, U

Title:
Synthesis of Peptides by Silver-Promoted Coupling of Carboxylates and Thioamides: Mechanistic Insight from Computational Studies

Date:
2016-02-24

Citation:
Hutton, C. A., Shang, J. & Wille, U. (2016). Synthesis of Peptides by Silver-Promoted Coupling of Carboxylates and Thioamides: Mechanistic Insight from Computational Studies. Chemistry A European Journal, 22 (9), pp.3163-3169. https://doi.org/10.1002/chem.201503753.

Persistent Link:
https://hdl.handle.net/11343/290865

Title: Synthesis of Peptides by Silver-Promoted Coupling of Carboxylates and Thioamides: Mechanistic Insight from Computational Studies

Authors: Uta Wille, PhD; Craig A Hutton; Jing Shang

To be cited as: 10.1002/chem.201503753

Link to VoR: https://doi.org/10.1002/chem.201503753

Synthesis of Peptides by Silver-Promoted Coupling of Carboxylates and Thioamides: Mechanistic Insight from Computational Studies

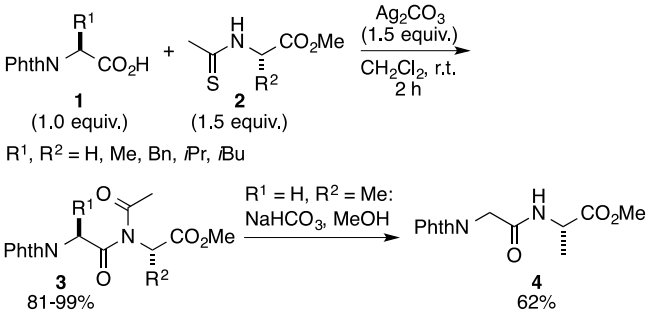
Craig A. Hutton,* Jing Shang, and Uta Wille*[a]

Abstract: The mechanism of the recently described N→C direction peptide synthesis through silver-promoted coupling of *N*-protected amino acids with thioacetylated amino esters was explored using density functional theory. Calculation of the potential energy surface for various pathways revealed that the reaction proceeds through silver-assisted addition of carboxylate **8** to thioamide **9**, which is followed by deprotonation and silver-mediated extrusion of sulphur as Ag_2S. The resulting isoimide is the key intermediate, which subsequently rearranges to an imide through a concerted pericyclic [1,3]-acyl shift (*O*-sp^2*N* 1,3-acyl migration). The proposed mechanism clearly emphasizes the requirement of two equivalents of Ag(I) and basic reaction conditions, which is in full agreement with the experimental findings. Alternative rearrangement pathways involving only one equivalent of Ag(I) or through *O*-sp^3*N* 1,3-acyl migration can be excluded. The computations further revealed that peptide couplings involving thioformamides require significant conformational changes in the intermediate isoformimide, which slow down the rearrangement process.

Introduction

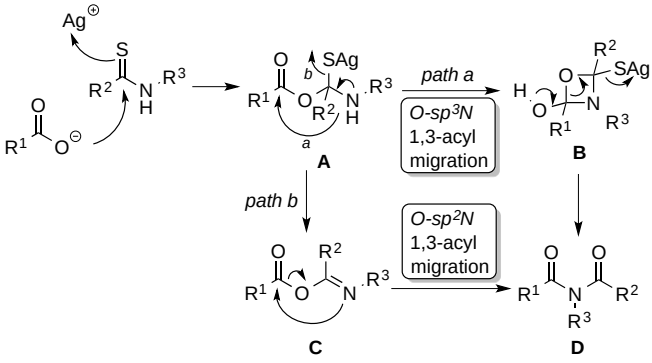
A central goal in peptide synthesis is the development of methods that enable the coupling of amino acids or peptides under mild conditions with high chemo- and stereoselectivity.[1] The desire for chemoselectivity has led to the development of methods that incorporate surrogates for the standard amine and carboxylate coupling partners, such as isonitriles,[2] azides,[3,4] sulfonamides,[5] thioacids[3,6] and thioesters.[4,7] A common theme in the development of such surrogate coupling partners is the use of sulphur-containing functional groups.

The laboratory of one of us recently developed a new method to achieve peptide coupling in the N→C direction through the silver-promoted ligation of *N*-protected amino acids **1** and thioacetylated amino esters **2**. The reaction involves a rearrangement of the molecular framework and leads to imides **3** in excellent yields, which could be converted into dipeptides **4** through selective hydrolytic removal of the *N*-acetyl group (Scheme 1).[8] The imides **3** are obtained as single stereoisomers under very mild conditions without evidence of epimerization. To demonstrate the scope of this methodology, synthesis of the pentapeptide thymopentin was successfully accomplished through a series of iterative N→C couplings.[8]



Scheme 1. Peptide coupling through Ag(I) promoted ligation of *N*-protected amino acids **1** with thioacetylated amino esters **2**.

The coupling of thioamides with carboxylic acids to yield the imide product after rearrangement requires a thiophilic metal (typically Ag(I), though Hg(II) is also suitable) and basic reaction conditions (e.g., Ag_2CO_3 or $AgNO_3$ + NEt_3). The highest yields of imides are obtained when both thioamide and Ag_2CO_3 are used in excess (1.5 equivalents). Proposed mechanisms of this reaction are outlined in Scheme 2.[8]



Scheme 2. Proposed mechanism for the formation of imides **3** through Ag(I) mediated coupling of carboxylates with thioamides (see ref. [8]).

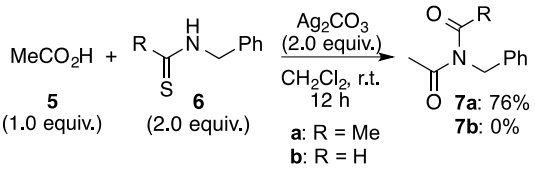
Coordination of Ag(I) to the thioamide should activate the latter for addition of the carboxylate, which leads to the tetrahedral adduct **A**. Rearrangement to imide **D** could proceed through an

[a] Assoc. Prof. C. A. Hutton, Ms. J. Shang, Assoc. Prof. U. Wille
School of Chemistry and Bio21 Institute
The University of Melbourne
30 Flemington Road, Parkville, VIC 3010, Australia
E-mail: chutton@unimelb.edu.au; uwille@unimelb.edu.au

Supporting information for this article is given via a link at the end of the document.

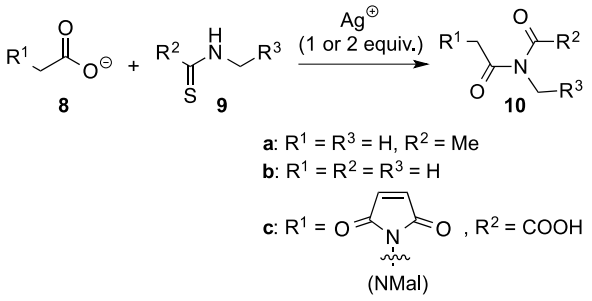
O-sp³N 1,3-acyl migration, likely via a four-membered intermediate **B** (path a). Alternatively, heterolytic cleavage of the C–S bond in **A** could lead to the isoimide intermediate **C**,[9] which could rearrange to **D** through a *O-sp²N* 1,3-acyl migration, as reported previously.[10] A recent computational study by Houk and Danishefsky *et al*. on the closely related isoformimide system (R^2 = H) revealed that the rearrangement **C→D** should, in fact, be considered as a concerted pseudopericyclic [1,3]-acyl shift.[11,12]

Whereas Danishefsky's reaction system requires forcing conditions (e.g., microwave irradiation at 150°C),[2a,13] the procedure outlined in Scheme 1 leads to rapid formation of imides **3** at room temperature after only two hours. However, further investigations by us revealed an unexpectedly drastic influence of the thioamide on the reaction outcome (Scheme 3). Thus, when *N*-benzylthioacetamide (**6a**) was treated with silver acetate in dichloromethane at ambient temperature, the imide **7a** was obtained in 76% yield. On the other hand, under the same conditions the reaction involving the *N*-benzylthioformamide (**6b**) yielded no imide product **7b**.[14]



Scheme 3. Ag(I) promoted coupling of acetate with thioamides.

Because of the significant synthetic potential of this new method for N→C direction peptide coupling, a fundamental understanding of the reaction mechanism is crucial. We have therefore employed density functional theory (DFT) calculations to explore the mechanism of this reaction in detail, using the reaction of the carboxylates **8** with thioamides **9** to give the imides **10** as model systems (Scheme 4).



Scheme 4. Model systems studied in this work.

The computations were aimed to reveal in particular: (i) The role of Ag(I) and the stage of the *O–N* 1,3-acyl migration; and (ii) the reason for the failure of the coupling in the case of thioformamides.

Results and Discussion

1. Computational Methods

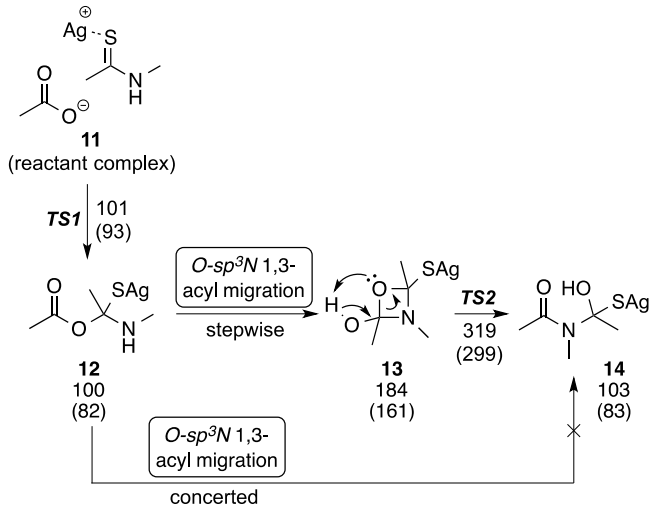
The calculations were carried out using the Gaussian 09 program.[15] Geometry optimizations and vibrational frequency analyses for all ground and transition state structures were performed using the B3LYP,[16] M06 and M06-2X[17] density functional theory methods, in combination with the 6-311G** and 6-311++G** basis sets[18] for all main group atoms and the SDD[19] and LANL2DZ[20] effective core basis set for Ag. Calculations in dichloromethane were performed for selected reactions using the Conductor-like Polarizable Continuum Model (CPCM).[21] All transition states showed only one imaginary frequency. Free energies given in this work include zero-point vibrational energy correction (ZPE), which was not scaled. The archive entries of the Gaussian output files for all optimized stationary points are available as electronic Supporting Information.

2. Rearrangement through *O-sp³N* 1,3-acyl migration

2.1 Reaction in the presence of one equivalent of Ag(I)

The coupling of acetate (**8a**) with *N*-methyl thioacetamide (**9a**) to produce imide **10a** was used as simplified model system to mimic the peptide coupling in Scheme 1. Scheme 5 shows the possible reaction pathway in the presence of one equivalent of Ag(I) including the free energy changes (ΔG) for the gas phase and in dichloromethane calculated with M06-2X/6-311++G**, using SDD for Ag. The optimized geometries for the reactant complex **11**, the transition state for the addition, ***TS1***, and the resulting adduct **12** for both gas phase and in dichloromethane are shown in Figure 1. The geometries of all other species are given in Figure S1 in the Supporting Information.

The reaction proceeds through formation of an association complex **11** between carboxylate **8a**, thioamide **9a** and Ag(I), which is about 820 kJ mol^{-1} lower in energy than the free reactants (not shown). The ΔG values in Scheme 5 are given relative to complex **11**. In this complex Ag(I) coordinates to both the thioamide sulphur and one carboxylate oxygen in nearly symmetrical fashion (Figure 1), thereby pre-arranging the system for the subsequent addition. This coordination pattern is, in fact, maintained throughout the entire sequence, where the distance between S and Ag is about 0.07 Å longer than the S–Ag bond calculated for Ag_2S.



Scheme 5. Addition of acetate (**8a**) to *N*-methyl thioacetamide (**9a**) and subsequent *O*-sp^3*N* 1,3-acyl migration in the presence of 1 equiv. of Ag(I). M06-2X/6-311++G** (SDD for Ag) free energies (ΔG) in kJ mol^{-1} relative to the reactant complex **11** for the gas phase and in dichloromethane (in brackets). A transition state for the cyclization **12**→**13** was not calculated (see text).

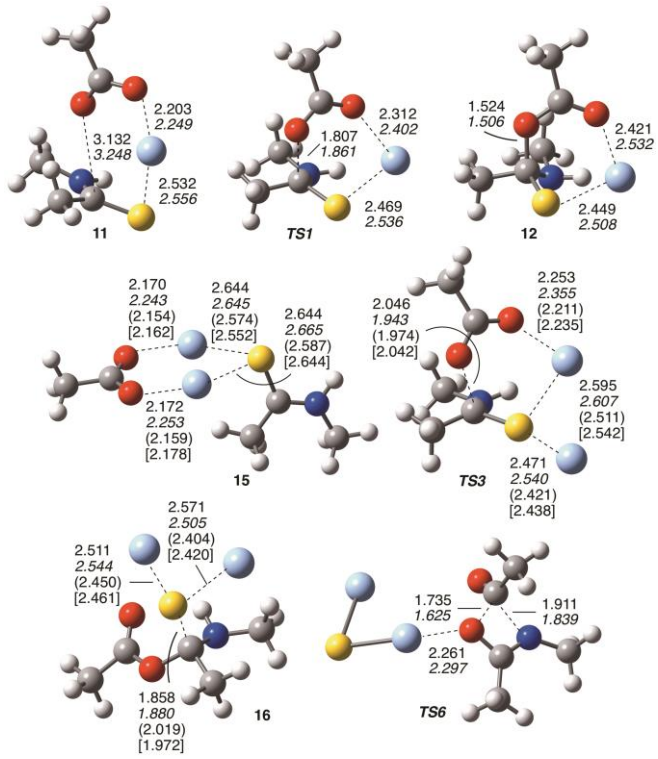


Figure 1. Selected optimised ground and transition state geometries. Distances in Å for geometries in the gas phase (normal) and in dichloromethane (italics) calculated with M06-2X/6-311++G** using SDD for Ag(I). Distances in brackets from B3LYP/6-311++G** calculations using SDD for Ag(I); distances in square brackets from M06/6-311++G** calculations using LANL2DZ for Ag(I).

The addition of acetate **8a** to the thioamide **9a** proceeds through ***TS1***, which is associated with an activation barrier of ca. 100 kJ mol^{-1}. Formation of adduct **12** is considerably endothermic, with the latter sitting in a very shallow well that lies just a few kJ mol^{-1} below ***TS1***. It is important to note that the B3LYP method failed to locate **12** and only revealed dissociation into the reactant complex **11**. Because of this, B3LYP data are excluded from the discussion of this pathway.

As would be expected for reactions involving ions, the computed stationary points in dichloromethane are generally about 10-20 kJ mol^{-1} below those for the gas phase, with the geometries exhibiting also slightly longer O–Ag and S–Ag coordination distances in solution (see Figure 1).

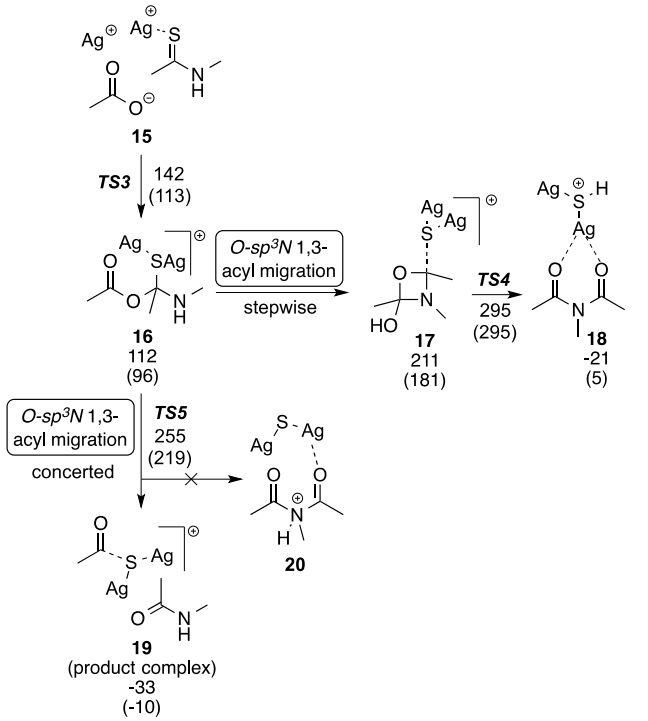
Adduct **12** could principally rearrange to imide **10a** through *O*-sp^3*N* 1,3-acyl migration via a sequential cyclization/ fragmentation. However, the computations predict that cyclization of N onto the acetate carbonyl to give the strained four-membered intermediate **13** is strongly endothermic. Because this cyclisation also involves concurrent protonation and deprotonation steps, a transition state was not calculated. Subsequent ring opening of **13** through ***TS2*** could lead to the desired rearranged framework. According to the calculations, this barrier is about 130 kJ mol^{-1} higher in energy than **13**. In fact, intrinsic reaction coordinate (IRC) calculations to explore the connectivity of ***TS2*** showed that breaking of the C–O bond occurs simultaneously with migration of the proton from the hydroxyl group and leads to formation of imide **14**, in which one of the carbonyl groups is truncated as hemithioacetal. It is reasonable to assume that, if such a reaction were to occur, compound **14** would rapidly hydrolyse to imide **10a**.

Alternatively, rearrangement of adduct **12** to **14** might also proceed through a concerted *O*-sp^3*N* 1,3-acyl migration with simultaneous scission of the *O*-acyl and formation of the N-acyl bond. However, a transition state for such process could not be located.

2.2 Reaction in the presence of two equivalents of Ag(I)

We next explored whether *O*-sp^3*N* 1,3-acyl migration could be a feasible pathway in the presence of two equivalents of Ag(I). The calculated ΔG values for the reaction of acetate (**8a**) with *N*-methyl thioacetamide (**9a**) relative to the reactant association complex **15** are given in Scheme 6. The optimized geometries for **15**, the transition state for the addition, ***TS3***, and the resulting adduct **16** for both gas phase and in dichloromethane are included in Figure 1. Geometries of the other species can be found in Figure S2 in the Supporting Information.

According to the calculations, the initial addition of **8a** to **9a** has no apparent benefit from the presence of two Ag(I). In fact, the barrier associated with this process, ***TS3***, is ca. 20–30 kJ mol^{-1} higher than ***TS1*** for the addition involving only one Ag(I). Likewise, the resulting adduct **16** is energetically slightly less favourable than its counterpart **12** (see Scheme 5).



Scheme 6. Addition of acetate (**8a**) to *N*-methyl thioacetamide (**9a**) and subsequent *O*-sp^3*N* 1,3-acyl migration in the presence of 2 equiv. of Ag(I). M06-2X/6-311++G** (SDD for Ag) free energies (ΔG) in kJ mol^{-1} relative to the reactant complex **15** for the gas phase and in dichloromethane (in brackets). A transition state for the cyclization **16**→**17** was not calculated (see text).

In order to exclude that this finding was an artefact of the theoretical method, we calculated the coupling reaction **15**→**16** at different levels of theory. The results are compiled in Table 1.

It appears that the B3LYP method predicts not only considerably higher energies for both ***TS3*** and **16**, compared to the M06(2X) methods, but also different geometries, in particular for adduct **16** (Figure 1). Thus, B3LYP calculates a C–S distance in **16** of 2.019 Å for the gas phase, clearly indicating dissociation into Ag_2S and a positively charged carboxylate–thioamide adduct. In contrast, the M06-2X computations reveal a shorter C–S bond of about 1.858 Å for the gas phase, or 1.880 Å in dichloromethane, respectively. The advanced dissociation in **16** predicted by B3LYP would explain the strong endothermicity associated with its formation, which lies energetically only slightly below ***TS3***. Because of this and the failure to locate adduct **12** (see above), we consider the B3LYP method unsuitable for the computational investigation of this reaction system. On the other hand, both M06 and M06-2X with the SDD or LANL2DZ basis set for Ag(I) perform comparably, in particular when the subsequent rearrangement via *O*-sp^2*N* 1,3-acyl migration is also considered (see below).

The predicted higher barrier for ***TS3*** compared to ***TS1*** can be rationalized by the fact that in reactant complex **15** the two Ag(I) coordinate to both oxygen atoms of carboxylate **8a** and the sulphur atom in thioamide **9a**, which keeps both reactants at distance. A considerable and energetically costly reorganisation of this coordination network is required for the addition to occur. Calculations revealed that a reactant association complex where only one acetate oxygen is coordinated to Ag (similar to complex **11**), is about 80 kJ mol^{-1} less favourable than **15** (not shown). The role of Ag coordination for the addition process will be discussed further in section 5.

Table 1. Calculated ΔG values of ground and transition states (in kJ mol^{-1}) for the addition of acetate (**8a**) to *N*-methyl thioacetamide (**9a**) and subsequent *O*-sp^2*N* 1,3-acyl migration in the presence of 2 equiv. of Ag(I).[a]

Method[a]	***TS3***[a]	**16**[a]	***TS6***[b]	**10a•2Ag**[b]
B3LYP/6-311G**, SDD (Ag^+)	159	150	76	-25
B3LYP/6-311++G**, SDD (Ag^+)	158	151	76	-23
B3LYP/6-311++G**, SDD (Ag^+), in CH_2Cl_2	134	132	68	-42
M06-2X/6-311++G**, SDD (Ag^+)	142	112	103	-21
M06-2X/6-311++G**, SDD (Ag^+), in CH_2Cl_2	113	96	83	-53
M06/6-311++G**, LANL2DZ (Ag^+)	125	89	92	-25
B3LYP/6-311G** [c]	--	--	77	-22
M06-2X/6-311++G** [c]	--	--	92	-25

[a] Energies relative to reactant association complex **15**. [b] Energies relative to **21a•2Ag**. [c] In the absence of Ag_2S (see text).

Similar to the mechanism involving one Ag(I), rearrangement of adduct **16** to imide **10a** through stepwise cyclization/ fragmentation is not feasible. Not only is formation of the strained four-membered intermediate **17** endothermic by more than 100 kJ mol^{-1}, but the subsequent ring opening via ***TS4*** requires an additional 80 kJ mol^{-1}, rendering this pathway kinetically impossible – despite the fact that formation the [imide–Ag_2SH^+] complex **18** is in principle thermodynamically favourable.

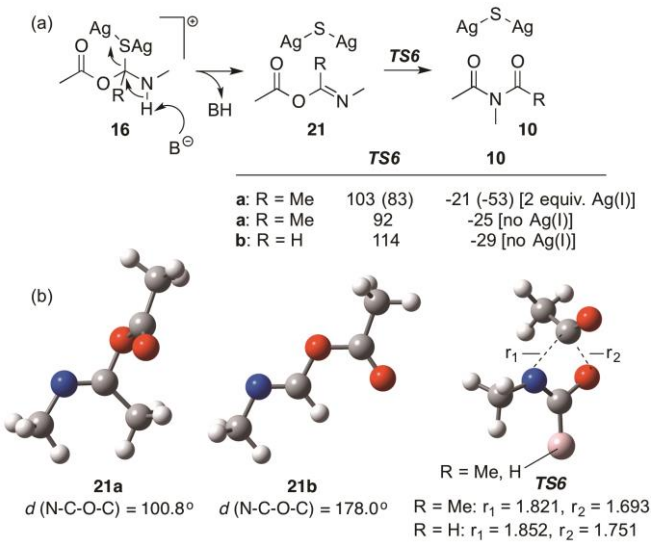
In contrast to the reaction in the presence of one equivalent of Ag(I), the transition state, ***TS5***, for a concerted *O*-sp^3*N* 1,3-acyl migration could be located for the reaction system involving two equivalents of Ag(I). However, such a rearrangement is not only associated with a high barrier, but also does not lead to the desired (protonated) imide **20**. IRC calculations show that ***TS5*** is the transition state of a 1,3-acyl migration, where C–N bond formation is immediately followed by fragmentation to give *N*-methyl acetamide and thioacetate (product complex **19**). While the geometry of ***TS5*** obtained for the gas phase shows an equal distance between the acyl fragment and the oxygen and nitrogen centre, the calculations in dichloromethane revealed a

later transition state with a considerably shorter N–acyl and longer O–acyl distance (see Figure S2).

To conclude, the calculations clearly show that, irrespective of the number of Ag(I) equivalents, rearrangement through *O–sp³N* 1,3-acyl migration is not possible.

3. Rearrangement through *O-sp²N* 1,3-acyl migration

Although the B3LYP method is considered as not suitable for studying this reaction (see above), the advanced dissociation of the C–S bond in adduct **16** predicted by this method might involuntarily hint to the reaction mechanism. In fact, the M06-2X computations also reveal elongation of the C–S bond in **16** by about 8% compared to the thioamide C–S bond in the reactant complexes **11** and **15** (ca. 1.72 Å), thereby rendering the C atom positively polarized. This suggests that two Ag(I) ions mediate extrusion of sulphur as Ag_2S, similar to a previous proposition by Avalos *et al*.[9] Under the basic reaction conditions this leads to the isoacetimide **21a** following deprotonation of the amide nitrogen, as shown in Scheme 7a (calculated as association complex with Ag_2S; the optimized geometries are shown in Figure S3). In contrast to this, no such stable 'leaving group' can be formed in adduct **12**, which exhibits a slightly shorter C–S bond (1.822 Å for the gas phase) than **16.**



Scheme 7. (a) Rearrangement of adduct **16** through *O–sp²N* 1,3-acyl migration of isoimide **21** in the presence of 2 equiv. of Ag(I). M06-2X/6-311++G** (SDD for Ag) free energies (ΔG) in kJ mol^{-1} relative to isomide **21** for the gas phase and in dichloromethane (in brackets). (b) Selected optimised geometries of isoimides **21** and ***TS6*** calculated with M06-2X/6-311++G** in the absence of Ag_2S.

Isoimide **21a** rearranges to imide **10a** in an exothermic process *via* ***TS6***, which is the transition state for a concerted, pericyclic 1,3-acyl shift, similar to that recently reported by Houk and Danishefsky *et al*.[11] According to the data in Table 1 this rearrangement is both kinetically and thermodynamically more favourable in dichloromethane, compared to the gas phase, with the energies from the B3LYP computations being about 20 kJ mol^{-1} below those obtained with the M06-2X density functional. Based on the findings for the addition reaction, however, the B3LYP results should be treated with caution. According to the M06-2X calculations, the rearrangement is not significantly influenced by the presence of Ag_2S, which rather assumes the role of a 'spectator' in this process. One of the Ag atoms coordinates to the oxygen atom of the acetimidate fragment in ***TS6*** (Figure 1), which leads to a slightly looser transition state than in the absence of Ag_2S (Scheme 7b) and raises the activation barrier by about 10 kJ mol^{-1}.

It should be noted that an analogous *O–sp²N* 1,3-acyl migration is highly unlikely for deprotonated **12**. The calculations show that the latter is not a stable structure, but dissociates into acetate (**8a**) and the thioacetamide anion **9a**$^-$ (data not shown).

The computations suggest for the model reaction of **8a** with **9a** that the acetate addition to the thioamide is assisted by one Ag(I). Once adduct **12** is formed, a second Ag(I) is required to mediate elimination of sulphur from the addition product (as Ag_2S). The resulting isoimide **21a** is the key intermediate, which rearranges to imide **10a** through *O–sp²N* 1,3-acyl migration.

4. Comparison of acetyl and formyl *O–sp²N* 1,3-acyl migrations

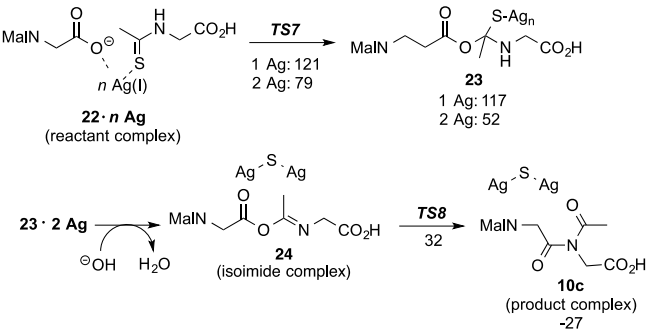
In order to gain understanding why imides could not be obtained through Ag(I) mediated coupling of acetate with thioformamides at room temperature (see Scheme 3),[14] we calculated the potential energy surface for the *O–sp²N* 1,3-acyl migration **21**→**10** for both the isoacetimide (**21a**) and isoformimide (**21b**)[22] system in the absence of Ag_2S.

The data in Scheme 7a show that, while the reaction is similarly exothermic for both systems, the barrier associated with ***TS6*** is higher by about 22 kJ mol^{-1} for the rearrangement of **21b**, compared to that for **21a**. The structure of ***TS6*** is similar for both systems, with the forming C–N and C–O bonds being both slightly larger for R = H than for R = Me (Scheme 7b). However, in both cases the forming C–O bond is shorter than the forming C–N bond, indicating a concerted but slightly asynchronous process. The higher rearrangement barrier likely results from a different structure of the isoformimide (**21b**). Whereas the isoformimide is planar [dihedral angle *d* (N-C-O-C) = 178°] due to hydrogen bonding between the imine proton and the carbonyl group, in isoacetimide (**21a**) the bulky 'central' methyl group twists the ester and imine moieties into an essentially perpendicular arrangement [*d* (N-C-O-C) ca. 101°]. This structural pre-organization in the isoacetimide is beneficial for the progression to ***TS6*** for the pericyclic reaction, which requires an orthogonal orbital arrangement.[11] Compared with the isoformimide, the structure of the isoacetimide is much closer to the 'reactive' geometry and does not require considerable structural or conformational changes, in particular the breaking of a hydrogen bond. We believe that similar conformational changes during the related isoformimide→formimide *O–sp²N* 1,3-acyl rearrangement in Danishefsky's system provide a reasonable explanation for the required forcing conditions.[2a,11-13]

With regards to this, it is worth noting that a stable ground state structure for the isoformimide **21b** with orthogonal ester and imine moieties (similar to the isoacetimide **21a**) could not be located.

5. Application to the 'real' system – synthesis of a dipeptide

We next extended our investigation to the synthesis of a dipeptide, in analogy to the experiments performed in our previous work.[8] Scheme 8 shows the reaction system, where *N*-glycyl maleimide **8c** (maleimide served as a simplified model for phthalimide that was used as *N*-protecting group in the experimental studies) was added to thioacetylated glycine **9c** (the free acid was used as a model for the methyl ester) in the presence of one and two equivalents of Ag(I). Selected structures and geometries are shown in Figure 2.



Scheme 8. Reaction of *N*-glycyl maleimide (**8c**) with thioacetylated glycine (**9c**) and rearrangement through *O*–sp^2*N* 1,3-acyl migration in the presence of 1 and 2 equiv. of Ag(I). M06-2X/6-311++G** (SDD for Ag) gas phase free energies (ΔG) in kJ mol^{-1} relative to the reactant complex **[22 · *n*Ag(I)]$^{(n-1)+}$** for ***TS7*** and **[23 · *n*Ag(I)]$^{(n-1)+}$,** and relative to **24** for ***TS8*** and **10c**.

Interestingly, in contrast to the simple model system (**8a** + **9a**) discussed above, the initial addition strongly benefits from the presence of two equivalents of Ag(I). Thus, ***TS7*** is energetically less favorable by about 40 kJ mol^{-1} in the presence of only one Ag(I) compared to two Ag(I). Likewise, in the presence of two Ag(I), formation of the adduct **23** is, although still endothermic, more likely to occur than if only one Ag(I) were present.

Inspection of the calculated structures reveals a rationale for this seemingly conflicting outcome. Thus, in contrast to the model reaction of **8a** with **9a** in the presence of two Ag(I), where both carboxylate oxygen atoms in the reactant complex **15** are 'deactivated' through coordination to silver, in reactant complex **[22 · 2 Ag]$^+$** one of the carboxylate oxygens exhibits a considerably weaker coordination with Ag(I) (the O–Ag distance is longer by about 0.3 Å than in **15**). The second Ag(I) is 'trapped' by a strong coordination with one oxygen atom of the maleimide protecting group and the sulphur atom of the thioamide, which brings both reactants together. It is worth noting that a reactant complex with a structure similar to **15** is about 10 kJ mol^{-1} less favourable. Thus, the weaker coordinated oxygen atom in **[22 · 2 Ag]$^+$** is 'available' to attack the thioamide **9c**. In contrast to this, the higher barrier associated with **[*TS7* · 1 Ag]**, compared with ***TS1*** could be due to steric interaction between one maleimide oxygen atom and a proton on the α-carbon of the thioamide moiety. These findings suggest a considerable influence of the *N*-protecting group for the success of the peptide coupling. Thus, coordination of Ag(I) to the carbonyl oxygen in imide or amide protecting groups should increase the availability of one carboxylate oxygen, which could increase the rate of the addition to the thioamide.

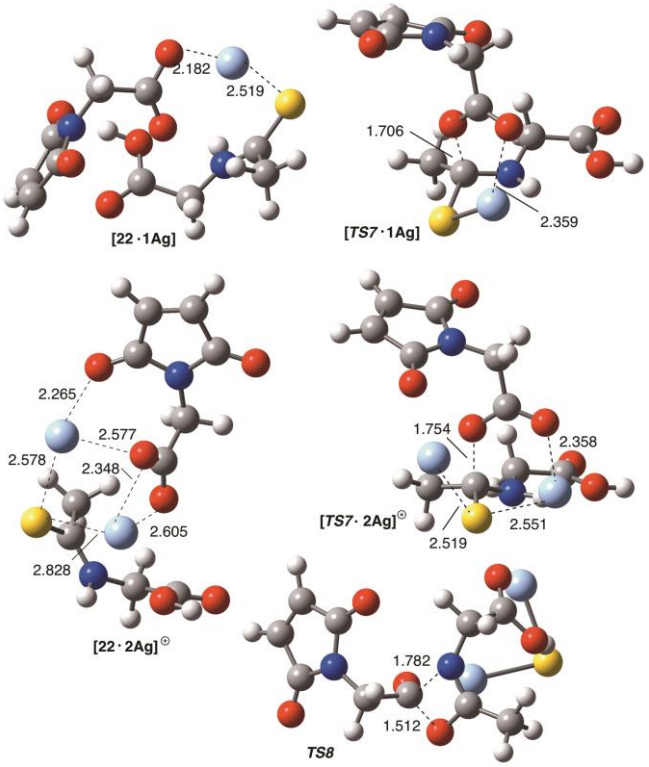


Figure 2. Selected optimised gas phase geometries of ground and transition states for the reaction of *N*-glycyl maleimide (**8c**) with thioacetylated glycine **9c** through *O*-sp^2*N* 1,3-acyl migration in the presence of 1 and 2 equiv. of Ag(I) calculated with M06-2X/6-311++G** using SDD for Ag(I). Distances in Å.

Elimination of Ag_2S and deprotonation leads to the isoimide **24**, which is followed by *O*–sp^2*N* 1,3-acyl migration through ***TS8***. This rearrangement is associated with a very modest barrier of only 22 kJ mol^{-1}, indicating a fast reaction in accordance with the experimental findings.[8] This is further supported by the unsymmetrical nature of the transition state, in which the O–acyl distance is considerably shorter than the N–acyl distance, indicating an early transition state. The considerably lower barrier of ***TS8*** compared to ***TS6*** for the reaction of **8a** with **9a** (see Scheme 7 and Table 1), could be explained by the stabilising effect of Ag_2S, which acts as a 'clamp' through coordination to the oxygen atoms of the carboxylate moiety

(2.516 Å) and the acyl fragment (2.273 Å) in ***TS8*** (distances omitted in Figure 2 for clarity).

Conclusions

DFT calculations were used to investigate the mechanism of the N→C direction peptide coupling through the silver-promoted ligation of *N*-protected amino acids with thioacetylated amino esters under basic conditions. Using simplified model systems, it was clearly revealed that a pathway involving *O*–sp^3*N* 1,3-acyl migration can be excluded in the presence of either one or two equivalents of Ag(I). The calculations show that the reaction proceeds through silver-assisted addition of the carboxylate **8** to the thioamide **9**, which is followed by deprotonation and silver-mediated extrusion of sulphur as Ag_2S. The resulting isoimide is the key intermediate, which subsequently rearranges to an imide through a concerted pericyclic [1,3]-acyl shift (*O*–sp^2*N* 1,3-acyl migration). Alternative pathways for the 1,3-acyl migration can be ruled out. The greatly differing rates of the closely related isoacetimide and isoformimide rearrangements are explained by conformational and hydrogen bonding effects in the ground states of the isoimides that result in a much lower energy barrier for the isoacetimide system.

While Ag(I) is not actively 'participating' in the actual acyl shift, its presence is crucial for mediating the initial carboxylate addition to the thioamide. Formation of the isoimide requires two equivalents of Ag(I) and basic reaction conditions, which is in excellent agreement with the experimental findings. The calculations also revealed insight into the role of coordination with Ag(I) for the addition and rearrangement process during the peptide coupling. Thus, an amide or imide protecting group for the *N*-terminus is predicted to increase the rate of the reaction by forming a tight coordination network with Ag(I) and the thioamide, leaving one carboxylate oxygen less coordinated and available for the addition to the thioamide. Further, Ag_2S leads to stabilization of the transition state of the rearrangement, ***TS8***, by acting as a 'clamp' through coordination to the oxygen atoms of the carboxylate moiety and the acyl fragment. Future experimental studies will reveal further insight into the role of *N*-protecting groups in directing the variety of plausible acyl transfer rearrangements during this coupling process.

Acknowledgements

This work was supported by the Australian Research Council and the National Computing Infrastructure (NCI).

Keywords: peptides • density functional calculations • reaction mechanisms • synthetic methods • rearrangement

[1] V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471–479.

[2] (a) X. Li, S. J. Danishefsky, *J. Am. Chem. Soc.* **2008**, *130*, 5446–5448. (b) Y. Rao, X. Li, S. J. Danishefsky, *J. Am. Chem. Soc.* **2009**, *131*, 12924–12926. (c) X. Wu, J. L. Stockdill, P. Wang, S. J. Danishefsky, *J. Am. Chem. Soc.* **2010**, *132*, 4098–4100.

[3] N. Shangguan, S. Katukojvala, R. Greenberg, L. J. Williams, *J. Am. Chem. Soc.* **2003**, *125*, 7754–7755.

[4] (a) E. Saxon, J. I. Armstrong, C. R. Bertozzi, *Org. Lett.* **2000**, *2*, 2141–2143. (b) B. L. Nilsson, L. L. Kiessling, R. T. Raines, *Org. Lett.* **2000**, *2*, 1939–1941.

[5] (a) D. Crich, K. Sana, S. Guo, *Org. Lett.* **2007**, *9*, 4423–4426. (b) D. Crich, I. Sharma, *Angew. Chem. Int. Ed.* **2009**, *48*, 7591–7594.

[6] (a) D. Crich, I. Sharma, *Angew. Chem. Int. Ed.* **2009**, *48*, 2355–2358. (b) D. Crich, K. Sasaki, *Org. Lett.* **2009**, *11*, 3514–3517. (c) P. Wang, S. J. Danishefsky, *J. Am. Chem. Soc.* **2010**, *132*, 17045–17051. (d) T. Wang, S. J. Danishefsky, *J. Am. Chem. Soc.* **2012**, *134*, 13244–13247.

[7] (a) P. E. Dawson, *Isr. J. Chem.* **2011**, *51*, 862–867. (b) L. Raibaut, N. Ollivier, O. Melnyk, *Chem. Soc. Rev.* **2012**, *41*, 7001–7015. (c) L. R. Malins, R. J. Payne, *Curr. Opin. Chem. Biol.* **2014**, *22*, 70–78. (d) J. Tailhades, N. A. Patil, M. A. Hossain, J. D. Wade, *J. Peptide Sci.* **2015**, *21*, 139–147.

[8] A. Pourvali, J. R. Cochrane, C. A. Hutton, *Chem. Commun.* **2014**, *50*, 15963–15966.

[9] (a) M. Avalos, R. Babiano, P. Cintas, C. J. Durán, F. J.; Higes, J. L. Jiménez, I. López, J. C. Palacios, *Tetrahedron* **1997**, *53*, 14463-14480. (b) M. Avalos, R. Babiano, C. J. Durán, J. L. Jiménez, J. C. Palacios, *Tetrahedron Lett.* **1994**, *35*, 477-480.

[10] (a) J. S. P. Schwarz, *J. Org. Chem.* **1972**, *37*, 2906-2908. (b) K. Brady, A. F. Hegarty, *J. Chem. Soc. Perkin 2* **1980**, 121-126. (c) A. F. Hegarty, N. M. Tynan, S. Fergus, *J. Chem. Soc. Perkin 2* **2002**, 1328-1334.

[11] G. O. Jones, X. Li, A. E. Hayden, K. N. Houk, S. J. Danishefsky, *Org. Lett.* **2008**, *10*, 4093-4096.

[12] Danishefsky *et al.* refer to the isoformimide as a formimidate–carboxylate mixed anhydride (FCMA).

[13] (a) X. Li, Y. Yuan, W. F. Berkowitz, L. J. Todaro, S. J. Danishefsky, *J. Am. Chem. Soc.* **2008**, *130*, 13222–13224. (b) X. Li, Y. Yuan, C. Kan, S. J. Danishefsky, *J. Am. Chem. Soc.* **2008**, *130*, 13225–13227.

[14] J. Shang, A. Pourvali, J. R. Cochrane, C. A. Hutton, *Aust. J. Chem.* **2015**, *in press.* DOI: 10.1071/CH15504.

[15] Gaussian 09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

[16] A. D. Becke, *J. Chem. Phys*. **1993**, *98*, 5648-5652.

[17] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215-241.

[18] (a) T. Clark, J. Chandrasekhar, G. W. Spitznagel, P. v. R. Schleyer, *J. Comp. Chem.* **1983**, *4*, 294-301. (b) M. J. Frisch, J. A. Pople, J. S. Binkley, *J. Chem. Phys.* **1984**, *80*, 3265-3269.

[19] (a) M. Dolg, U. Wedig, H. Stoll, H. Preuss, *J. Chem. Phys*. **1987**, *86*, 866–872. (b) D. Andrae, U. Haussermann, M. Dolg, H. Stoll, H. Preuss, *Theor. Chim. Acta* **1990**, *77*, 123–141.

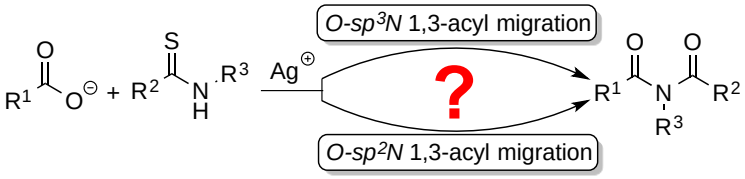
[20] P. J. Hay, W. R. Wadt, *J. Chem. Phys*. **1985**, *82*, 299–310.

[21] (a) V. Barone, M. Cossi, *J. Phys. Chem. A* **1998**, *112*, 1995–2001. (b) A. Klamt, G. Schüürmann, *J. Chem. Soc. Perkin Trans. 2* **1993**, 799–805.

[22] For comparison, we have also performed calculations using the B3LYP method, as previously used in ref. [11]. These calculations reveal ΔG values for the activation barrier that are lower by ca. 14 kJ mol^{-1}, and reaction energies lower by about 5 kJ mol^{-1} compared with the M06-2X method.

Entry for the Table of Contents

FULL PAPER



C. A. Hutton, J. Shang, U. Wille**

Page No. – Page No.

Synthesis of Peptides by Silver-Promoted Coupling of Carboxylates and Thioamides: Mechanistic Insight from Computational Studies

The mechanism of the N→C direction peptide synthesis through silver-promoted coupling of *N*-protected amino acids with thioacetylated amino esters was explored using density functional theory. The key step is rearrangement of the intermediate isoimide to an imide through a concerted pericyclic [1,3]-acyl shift (*O*–*sp*^{2}*N* 1,3-acyl migration).