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$RuCl_3$-promoted amide formation from azides and thioacids

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Abstract—Described here is the Ru(III)-promoted amide formation from azides and thioacids, which were shown not to form amides at room temperature in the absence of ruthenium. We believe that a complex formed by Ru(III) increases the reactivity of the thiocarbonyl species and therefore reaction with azides occurs at room temperature, even when less reactive (electron rich and/or sterically hindered) azides are employed.

The amide bond formation is one of the most studied reactions in organic chemistry: an activated carboxylic acid reacts with an amine to form the highly stable peptide bond. In 1988, a new method for the formation of amide bond was reported.[1] Azides were directly converted into amides by reaction with thioacids. The authors assumed that this reaction was initiated by traces of H_2S contained in thioacids, which might have reduced azides to amines. Recently, a revised mechanism has been proposed for this reaction.[2] A thiatriazoline intermediate, first formed from the azide and the thiocarboxylate, gives the corresponding amide together with nitrogen and sulfur as byproducts (Fig. 1). The authors have also excluded the formation of amines as reactive intermediates and have found that bases such as 2,6-lutidine accelerate this reaction. These new conditions work well in different solvents and yields are generally good to quantitative. One limitation

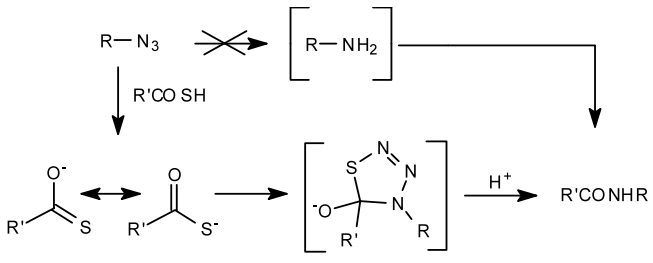

Figure 1. Mechanism of amide formation from azides and thioacids.

of this method, however, is the use of relatively harsh reaction conditions (60°C, 36 h), especially when less reactive azides were employed. We have recently applied this reaction to carbohydrate conjugation as a part of our effort to develop carbohydrate arrays. However, the use of high temperature and long reaction times can not be sustained by sensitive complex oligosaccharides for high-throughput generation of libraries in micro/nano-molar quantities (e.g. reaction in microtiter plates). We had employed the copper(I)-catalyzed 1,3-diplar cycloaddition[3] between alkynes and azides for the assembly of oligosaccharide microarrays in microtiter plates with very high yield.[4] This method is capable of high-throughput synthesis in aqueous solution at room temperature without protecting group manipulation, and the reaction product can be used for screening without isolation. The idea of microscale synthesis and screening in situ was also demonstrated in our previous work on amide formation from amines and acids.[5] We intend to develop another amide formation from thioacids and azides so that it can be carried out at room temperature for screening in situ. From the published results it was evident that electron-poor azides are more reactive to form amides, suggesting that the LUMO orbitals of the dipole are involved in the formation of the thiatriazoline intermediate. Two mechanisms are possible, either a concerted inverse-electron demand 1,3-diploar cycloaddition (IED 1,3-DC) or a two-step 'diazotransfer like' cyclization. It is known that both types of reactions can be accelerated by metals.[6] Indeed, we have found that ruthenium(III) promotes the amide formation from azides and thioacids. In this work, we only selected examples which do not (or poorly) form amides at room temper-

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ature under the reaction conditions reported before[2] and as a thioacid model we chose thiolacetic acid. 1-Azido-1-deoxy-β-D-glucose (Table 1, entry 1) was taken as first model study. This compound was converted, as reported, to the corresponding acetamide in 80% yield when heated in water at 60°C for 36 h. However, when this reaction was run at room temperature, a very slow conversion was observed, and after 18 h, no product could be isolated. We tested different concentrations of $RuCl_3$, and found that the optimal amount is 0.5 equivalents (Table 1, entry 1). Reactions were run both in water and methanol with comparable yields. Other examples of azides with poor reactivity without $RuCl_3$ are reported in Table 1 (entries 2–6). Examples for both protected and free sugar-azides are shown and in all cases, after 18 h at room temperature, high yields of the corresponding acetamides were isolated.[7] A few key experiments were then run to understand the pathway of this promoted reaction. When azides were reacted with $RuCl_3$/base, in the absence of thioacids, only starting material was recovered and no traces of the reduced amine were detected by NMR. Moreover, amines did not form the corresponding amide products under the same reaction conditions. These two additional experiments confirmed the revised mechanism for this amide formation. In Figure 2, a mechanism is proposed. Either in the concerted (IED 1,3-DC, path a) or diazotransfer like (path b) mechanism, ruthenium might form a complex with the thiocarbonyl species[8] and increase the electron density of the $HOMO_{dipolarophile}$ orbitals (Fig. 2).

This Ru(III)-promoted amide bond formation allows synthesis of amides from azides and thioacids at room temperature and the reaction is applicable to those with less reactive azides. This reaction is complimentary to the traditional amide forming reaction and should be useful for synthesis of amides without protecting group manipulation.

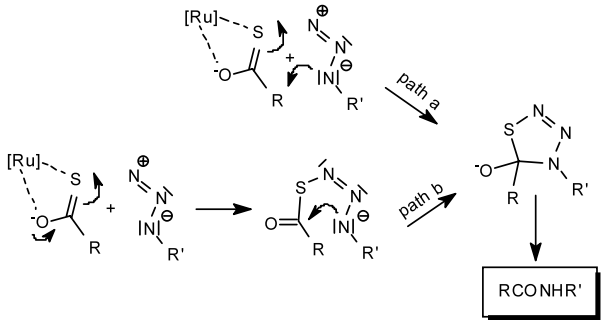
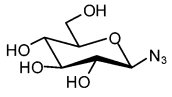
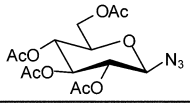
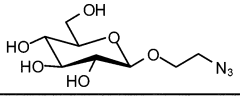
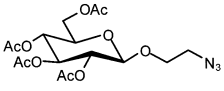
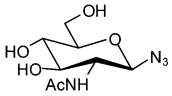
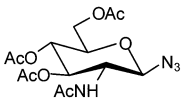


Figure 2. Ru(III)-promoted amide formation from thioacids and azide.

Table 1. Conversion of azides to acetamides at room temperature[a]

Entry	Azide	equiv. $RuCl_3$	Solvent	Isolated Yield
1		none	H_2O	0%
		0.1	H_2O	36%
		0.2	H_2O	66%
		0.3	H_2O	78%
		0.5	H_2O	88%
		0.1	MeOH	45%
		0.5	MeOH	91%
2		none	MeOH	0%
		0.2	MeOH	56%
		0.5	MeOH	80%
3		none	H_2O	25%
		0.2	H_2O	60%
		0.5	H_2O	85%
4		none	MeOH	9%
		0.2	MeOH	48%
		0.5	MeOH	80%
5		none	H_2O	0%
		0.5	H_2O	85%
6		none	MeOH	0%
		0.5	MeOH	78%

[a] Azide (0.2 M), thiolacetic acid (2.5 equiv.), 2,6-lutidine (2.5 equiv.), 18 h.

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7. General procedure for the $RuCl_3$-promoted amide formation: The starting azide (0.1 mmol) was dissolved in 500 μL of the suitable solvent (MeOH or H_2O, see Table 1). To this solution were added 2,6-lutidine (2.5 equiv.), thiolacetic acid (2.5 equiv.) and $RuCl_3$ (0.5 equiv.). The mixture was stirred at room temperature in a capped vial for 18 h, the catalyst was then removed by filtration and the crude product purified by flash chromatography on silica gel. 1-Acetamido-1-deoxy-β-D-glucose (**1**): FC: AcOEt/MeOH (4:1→1:1). Yield 91% (20 mg). ^{1}H NMR (CD_3OD): δ 3.81 (dd, 1H, $J=12.10$ Hz, $J=2.20$ Hz), 3.63 (dd, 1H, $J=12.10$ Hz, $J=5.50$ Hz), 3.38 (t, 1H, $J=9.16$ Hz), 3.33–3.27 (complex, 3H), 3.22 (t, 1H, $J=9.16$ Hz), 1.98 (s, 3H). ^{13}C NMR (CD_3OD): δ 174.44, 81.02, 79.59, 78.89, 73.88, 71.40, 62.69, 22.87. HR-MALDI-FTMS: calcd for $C_8H_{15}NO_6Na$ $[M+Na]^+$, 244.0792; found, 244.0794. 1-Acetamido-1-deoxy-2,3,4,6-tetraacetyl-β-D-glucose (**2**): FC: AcOEt/*n*-hexane (1:1)→AcOEt. Yield 80% (31 mg). ^{1}H NMR ($CDCl_3$): δ 6.29 (d, 1H, $J=9.39$ Hz), 5.27 (t, 1H, $J=9.68$ Hz), 5.21 (t, 1H, $J=9.39$ Hz), 5.02 (t, 1H, $J=9.68$ Hz), 4.88 (t, 1H, $J=9.68$ Hz), 4.28 (dd, 1H, $J=12.61$ Hz, $J=4.40$ Hz), 4.05 (dd, 1H, $J=12.61$ Hz, $J=2.34$ Hz), 3.79 (m, 1H), 2.04 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H), 1.96 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 171.05, 170.58, 170.36, 169.82, 169.55, 78.15, 73.46, 72.63, 70.53, 68.05, 61.57, 23.34, 20.53. HR-MALDI-FTMS: calcd for $C_{16}H_{23}NO_{10}Na$ $[M+Na]^+$, 412.1214; found, 412.1214. (2-Acetamido-ethyl)-β-D-glucopyranoside (**3**): FC: AcOEt/MeOH (4:1→1:1). Yield 85% (23 mg). ^{1}H NMR (CD_3OD): δ 4.26 (d, 1H, $J=7.70$ Hz), 3.90 (m, 1H), 3.86 (dd, 1H, $J=12.10$ Hz, $J=1.46$ Hz), 3.65 (m, 2H), 3.44 (m, 1H), 3.34 (m, 2H), 3.26 (m, 2H), 3.18 (dd, 2H, $J=9.16$ Hz, $J=7.70$ Hz), 1.94 (s, 3H). ^{13}C NMR (CD_3OD): δ 173.43, 104.49, 77.97, 77.94, 75.09, 71.58, 69.59, 62.66, 40.71, 22.55. HR-MALDI-FTMS: calcd for $C_{10}H_{19}NO_7Na$ $[M+Na]^+$, 288.1054; found, 288.1056. (2-Acetamido-ethyl)-2,3,4,6-tetraacetyl-β-D-glucopyranoside (**4**): FC: AcOEt/*n*-hexane (1:1)→AcOEt. Yield 80% (35 mg). ^{1}H NMR ($CDCl_3$): δ 5.94 (m, 1H), 5.18 (t, 1H, $J=9.68$ Hz), 5.04 (t, 1H, $J=9.68$ Hz), 4.96 (dd, 1H, $J=9.68$ Hz, $J=7.92$ Hz), 4.48 (d, 1H, $J=7.92$ Hz), 4.23 (dd, 1H, $J=12.32$ Hz, $J=4.98$ Hz), 4.13 (dd, 1H, $J=12.32$ Hz, $J=2.34$ Hz), 3.81 (m, 1H), 3.69 (m, 2H), 3.42 (m, 2H), 2.06 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H), 1.96 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 170.64, 170.26, 170.16, 169.60, 169.43, 100.94, 72.52, 71.93, 71.29, 69.35, 68.20, 61.75, 39.23, 23.16, 20.72, 20.58. HR-MALDI-FTMS: calcd for $C_{18}H_{27}NO_{11}Na$ $[M+Na]^+$, 456.1476; found, 456.1469. 1,2-Dicetamido-1,2-dideoxy-β-D-glucose (**5**): FC: AcOEt/MeOH (2:1). Yield 85% (22 mg). ^{1}H NMR (CD_3OD): δ 4.95 (d, 1H, $J=9.98$ Hz), 3.83 (dd, 1H, $J=11.74$ Hz, $J=1.76$ Hz), 3.73 (t, 1H, $J=9.98$ Hz), 3.65 (m, 1H), 3.47 (m, 1H), 3.33 (m, 2H), 1.96 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (CD_3OD): δ 174.38, 173.89, 80.30, 79.66, 76.26, 71.81, 62.64, 56.12, 22.84, 22.77. HR-MALDI-FTMS: calcd for $C_{10}H_{18}N_2O_6Na$ $[M+Na]^+$, 285.1057; found 285.1057. 1,2-Dicetamido-1,2-dideoxy-3,4,6-triacetyl-β-D-glucose (**6**): FC: AcOEt/MeOH (95:5). Yield 78% (30 mg). ^{1}H NMR ($CDCl_3$): δ 7.01 (d, 1NH, $J=8.44$ Hz), 6.21 (d, 1NH, $J=8.44$ Hz), 5.06 (m, 3H), 4.26 (dd, 1H, $J=12.83$ Hz, $J=4.40$ Hz), 4.11 (m, 1H), 4.05 (dd, 1H, $J=12.47$ Hz, $J=2.20$ Hz), 3.75 (m, 1H), 2.05 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.95 (s, 3H), 1.93 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 172.00, 171.84, 170.96, 170.71, 169.29, 80.18, 73.39, 72.91, 67.70, 61.73, 53.28, 23.36, 23.07, 20.73, 20.69, 20.57. HR-MALDI-FTMS: calcd for $C_{16}H_{25}N_2O_9$ $[M+H]^+$, 389.1554; found 389.1562.
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