Aza-Prins Reaction Promoted by Titanium Tetraiodide and Iodine

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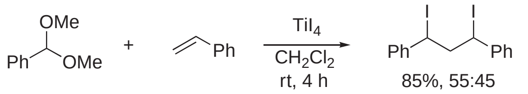
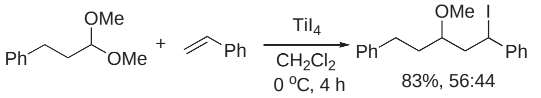
In the presence of titanium tetraiodide and iodine, olefins and acetylenes underwent aza-Prins reaction to give 1,3-iodoamines in good yields.

Prins and ene-type reactions provide us with important methodologies for the formation of homoallylic alcohol derivatives, where efficient C–C bond formations are realized.[1] Relating to these methodologies, we have already reported interesting C–C bond forming reactions using TiI_4 (eqs. 1 and 2).[2] Although there are several examples of aza-Prins-type reaction using iminium salts, only a limited number of literature is available for an imine version of the Prins and ene-reactions.[3]

We have recently embarked on the reactions using titanium tetraiodide, where the ability of titanium tetraiodide to iodinate and reduce organic molecules is responsible for the success of facile transformations.[4] During these investigations, we have been interested in the ability of titanium tetraiodide to induce hydroiodination of olefins and acetylenes to give iodoalkanes, 1,1-diiodoalkanes, and 2-iodoalkenes depending on the structure of substrate. This paper describes an intriguing aza-Prins reaction of olefins and acetylenes with imines promoted by titanium tetraiodide (eqs. 3 and 4).



(1)



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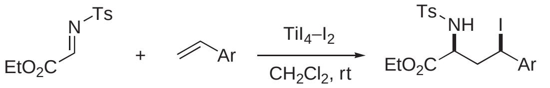

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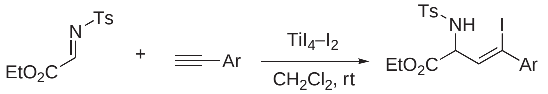
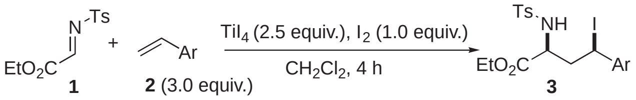


(4)

The aza-Prins reaction of a variety of olefins was carried out, and the results are summarized in Table 1. In the absence of iodine, the reaction gave the adduct **3** in only 34% yield, whereas the presence of the added iodine (1.0 equiv.) considerably improved the product yield (Entries 1 and 2). A similar effect of the additive was observed using $AgBF_4$ (1.0 equiv.) (Entry 4). One of the roles of additives may involve the formation of $I_3Ti^+I_3^-$, $I_3Ti^+BF_4^-$, or related species to increase the Lewis acidity of the titanium halides.

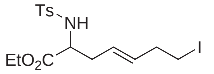
This reaction was sensitive to the amounts of the olefin and TiI_4, and the use of one equiv. of both reagents gave much reduced amount of the adduct **3** (<25%). Regarding the reaction temperature, the reaction at room temperature recorded a slightly better result in terms of the product yield and the diastereoselectivity (Entries 2 and 3). Other heteroaromatic derivatives served as nucleophiles to give the adducts in moderate yields (Entries 5–7). Vinylcyclopropane gave ring-opened iodinated product **4**,[5] albeit in low yield (Entry 8).

Table 1. Aza-Prins reaction of olefins promoted by TiI_4–I_2[a]



Entry	Ar	Temp./°C	Yield/%[b]	*syn*:*anti*[c]
1[d]	Ph	0	34	64:36
2	Ph	0	74	55:45
3	Ph	rt	79	63:37
4[e]	Ph	rt	75	59:41
5	1-Naphthyl	rt	58	59:41
6	2-Furyl	rt	42	61:39
7	2-Thienyl	rt	44	62:38
8	Cyclopropyl	rt	19[f]	—

[a]The reaction was carried out according to the typical experimental procedure. [b]Isolated yield. [c]Ratio determined by ^{1}H NMR and/or HPLC. Relative stereochemistry was established after converting into cyclized azetidine. [d]The reaction was carried out with TiI_4 (2.5 equiv.) in the absence of I_2. [e]The reaction was carried out with TiI_4 (2.5 equiv.) and $AgBF_4$ (1.0 equiv.) in the absence of I_2. [f]The ring-opened homoallylic iodide **4** was obtained.



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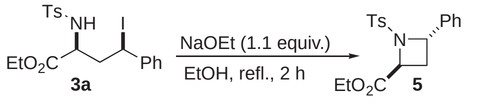
Cyclization of the adduct **3a** into azetidine **5** was readily carried out by treating with NaOEt in refluxing EtOH (Scheme 1).

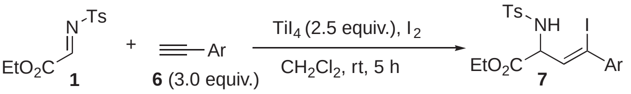
Under similar conditions found for the aza-Prins reaction of olefins, acetylenes also underwent addition reaction with the imine **1** to give vinyl iodides **7** in good yields. Table 2 summarizes the results.[6] Regarding the amount of added iodine, the use of a catalytic amount slightly increased the product yield and that of 1.0 equiv. gave the highest diastereoselectivity, whereas the best yield was obtained using 3.0 equiv. (Entries 1–3). In contrast to the cases with olefins, use of $AgBF_4$ did not give a comparable result to I_2 (Entry 4). Other aromatic acetylenes studied here also underwent aza-Prins reaction to give (*Z*)-vinyl iodides as major adducts in good yields.

Isomerization of the double bond of the resulting vinyl



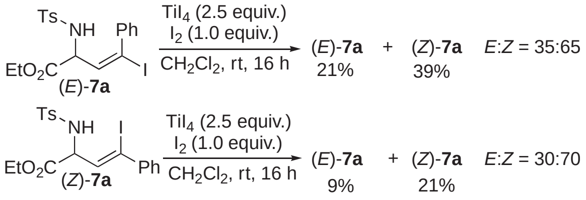
Scheme 1. Cyclization into azetidine.

Table 2. Aza-Prins reaction of acetylenes promoted by TiI_4–I_2[a]

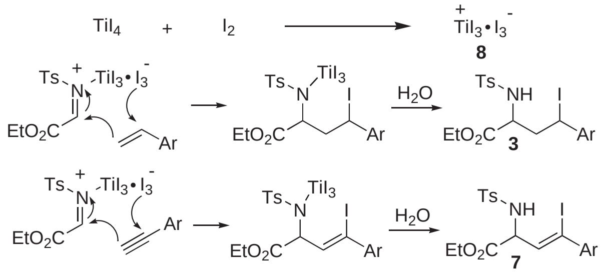


Entry	Ar	I_2/equiv.	Yield/%[b]	*Z*:*E*[c]
1	Ph	0.1	59	75:25
2	Ph	1.0	70	88:12
3	Ph	3.0	76	65:35
4	Ph	none[d]	53	84:16
5	Ph	none	56	73:27
6	4-$MeOC_6H_4$	3.0	64	58:42
7	4-MeC_6H_4	3.0	65	71:29
8	4-ClC_6H_4	3.0	84	77:23
9	4-BrC_6H_4	3.0	76	60:40

[a] The reaction was carried out according to the typical experimental procedure. [b] Isolated yield. [c] Ratio determined by ^{1}H NMR and/or HPLC. The geometry of the olefin was determined by ^{1}H NMR. [d] The reaction was carried out with TiI_4 (2.5 equiv.) and $AgBF_4$ (1.0 equiv.).



Scheme 2. Isomerization of the double bond.



Scheme 3. A possible reaction mechanism.

iodide was examined using the following experiments (Scheme 2). Subjection of both (*E*)- and (*Z*)-**7a** to the present aza-Prins reaction conditions gave a mixture of isomers. These results indicate that the isomerization took place to a certain extent under the present conditions.

Scheme 3 shows a possible reaction mechanism. First, the reaction of TiI_4 with I_2 may produce a complex **8** or related species, which in turn activates the imino nitrogen. Subsequent iodoethylation or iodoethenylation followed by protonation gives the adduct **3** or **7**, respectively. This cyclic transition state may explain the predominant formation of (*Z*)-olefin with respect to the adduct **7**. However, under the present conditions, involvement of the isomerization of (*Z*)-**7** into its (*E*)-isomer may reflect the isomer ratios.

In summary, we have developed a facile procedure for the aza-Prins reaction of olefins and acetylenes using TiI_4 and I_2 as a Lewis acid promoter to produce 1,3-iodoamines in good yields, where the use of iodine additive is crucial for the success of these intriguing and useful processes.

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This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday.

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6 A typical procedure is as follows: Under an argon atmosphere, to a suspension of TiI_4 (Soekawa Chemical Co., used after sublimation 278 mg, 0.50 mmol) and I_2 (152 mg, 0.60 mmol) in CH_2Cl_2 (1.0 mL) were added simultaneously solutions of the imine **1** (51.8 mg, 0.20 mmol) in CH_2Cl_2 (1.0 mL) and phenylacetylene (61.3 mg, 0.60 mmol) in CH_2Cl_2 (1.0 mL) at rt during 3 h using a microfeeder. After stirring at rt for 2 h, the mixture was quenched by the addition of sat. $NaHCO_3$ (aq) and $NaHSO_3$ (aq) (5%). The mixture was filtered through a Celite pad. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (aq) and brine, and then dried over anhydous Na_2SO_4. Purification on silica gel TLC (Hexane/PhMe/AcOEt = 2/2/1) gave the adducts (*Z*)-**7** (49.1 mg, 49%) and (*E*)-**7** (26.2 mg, 27%) as yellow oils. (*Z*)-**7**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.24 (t, $J = 7.1$ Hz, 3H), 2.37 (s, 3H), 4.16 (q, $J = 7.1$ Hz, 2H), 4.94 (dd, $J = 6.6$, 8.7 Hz, 1H), 5.52–5.65 (m, 2H, including a doublet at 5.60 ($J = 8.7$ Hz, 1H)), 7.18–7.29 (m, 7H), 7.80–7.83 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.0, 21.5, 62.6, 62.7, 110.6, 127.6, 128.2, 128.5, 129.1, 129.7, 132.0, 137.0, 141.9, 143.8, 168.8. (*E*)-**7**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.23 (t, $J = 7.1$ Hz, 3H), 2.41 (s, 3H), 4.11 (q, $J = 7.1$ Hz, 2H), 4.40 (dd, $J = 6.6$, 9.6 Hz, 1H), 5.40 (d, $J = 6.6$ Hz, 1H), 6.13 (d, $J = 9.6$ Hz, 1H), 7.22–7.25 (m, 2H), 7.31–7.36 (m, 5H), 7.51–7.54 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.9, 21.5, 55.8, 62.7, 103.0, 127.2, 128.3, 128.5, 128.9, 129.6, 135.1, 136.7, 140.3, 143.7, 168.6. For the assignment of the olefin geometries, see: D. P. Curran, D. Kim, *Tetrahedron* **1991**, *47*, 6171; P. J. Kropp, S. D. Crawford, *J. Org. Chem.* **1994**, *59*, 3102.

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