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TITANIUM TETRAIODIDE INDUCED CYCLIZATION OF 2-(2-CYANOALK-1-ENYL)- β -KETO ESTERS INTO 2-IODOPYRIDINES

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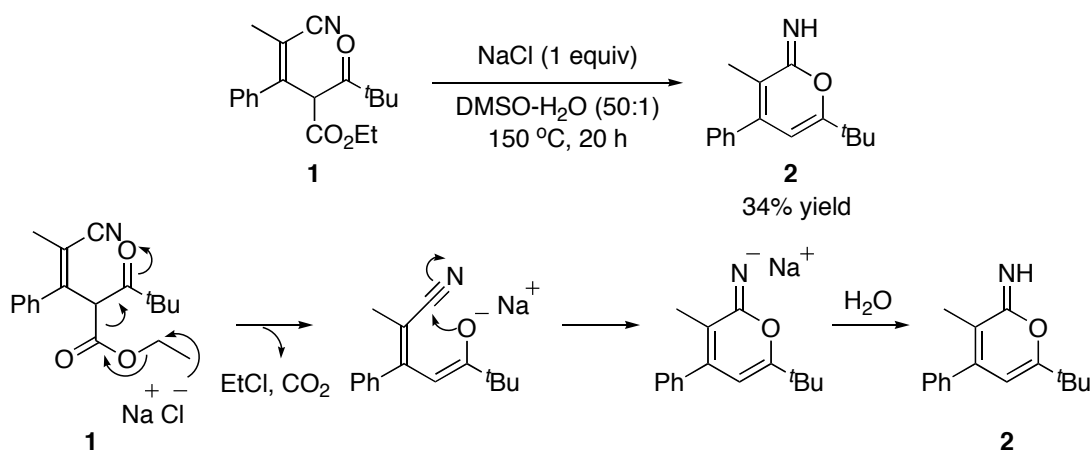
Abstract – Highly substituted 2-iodopyridines were synthesized from 2-(2-cyanoalk-1-enyl)- β -keto esters under the influence of titanium tetraiodide that worked efficiently for iodination-cyclization.

Among the pyridine derivatives 2-halopyridines have been utilized as useful intermediates for the nucleophilic displacements of halogens with several nucleophiles and for the lithiation with *n*-butyllithium at low temperature to generate lithiopyridines, which react with several electrophiles.¹ During investigation into the intriguing heterocycle formations using conjugate addition reactions to alkynyl imines² and their ketone analogues,³ we found a facile 2-iodopyridine formation from 2-(2-cyanoalk-1-enyl)- β -keto esters with titanium tetraiodide which has both a good iodination ability and mild Lewis acidity. This paper reports a short-step 2-iodopyridine synthesis.

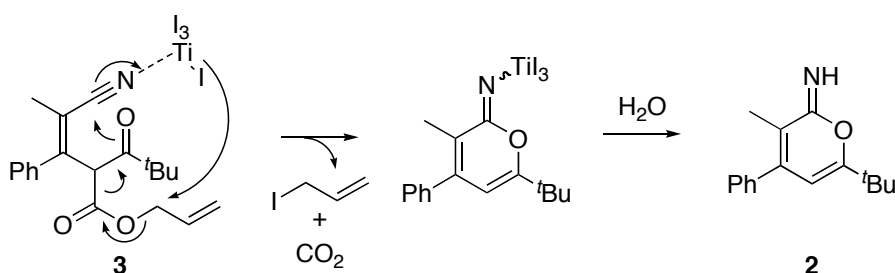
Regarding other nitrogen-containing heterocycles, we found that the decarboxylation-cyclization reaction of 2-(2-cyanoalk-1-enyl)- β -keto ester (**1**)⁴ gave 2-iminopyrone (**2**) (Scheme 1). The decarboxylation was carried out in the presence of one equivalent of sodium chloride in DMSO-H₂O (50:1) at 150 °C for 20 h to give 2-iminopyrone (**2**) in 34% yield.^{3b,5} Decarboxylation reactions using other metal chlorides such as LiCl and KCl did not improve the yield of 2-iminopyrone (**2**). Since iodide anion often induced removal of an allylic moiety, decarboxylation-cyclization reaction of β -keto allyl ester (**3**) was next examined using TiI₄ by a reaction mechanism as shown in Scheme 2.⁶ The reaction of cyano- β -keto allyl ester (**3**) with TiI₄ (1.7 equiv) was carried out in CH₂Cl₂ at rt for 20 h to give 2-iodopyridine (**4**) in 12% yield along with the recovered cyano- β -keto allyl ester (**3**) in 52% yield (Table 1, entry 1). Although 2-iminopyrone (**2**) was not obtained, the present 2-iodopyridine synthesis was investigated in detail due to the importance of this class of compounds.^{7,8} On the other hand, the reaction of cyano- β -keto allyl ester (**3**) with TiCl₄

This paper is dedicated to the memory of Dr. John Daly.

(1.0 equiv) or TiBr_4 (1.7 equiv) did not give the 2-chloro or 2-bromopyridines, and β -keto allyl ester (**3**) was recovered in 97% and 93% yields, respectively. In order to improve the yield of the 2-iodopyridine (**4**), the use of additives was next examined. When $\text{Ti}(\text{O}^i\text{Pr})_4$ was used as an additive, 2-iodopyridine (**4**) was obtained in 32% yield (entry 2).⁹ Although other titanium alkoxides were examined, the product yields were not satisfactory (entries 2-6). Among other additives besides titanium alkoxides, salicylic acid was found to be the most effective.^{9a} When both $\text{Ti}(\text{OEt})_4$ (0.25 equiv) and salicylic acid (1.0 equiv) were used as additives, 2-iodopyridine (**4**) was obtained in 52% yield (entry 7). Finally, the combined use of $\text{Ti}(\text{OEt})_4$ (0.25 equiv) and salicylic acid (2.0 equiv) as additives gave 2-iodopyridine (**4**) in 61% yield (entry 8).

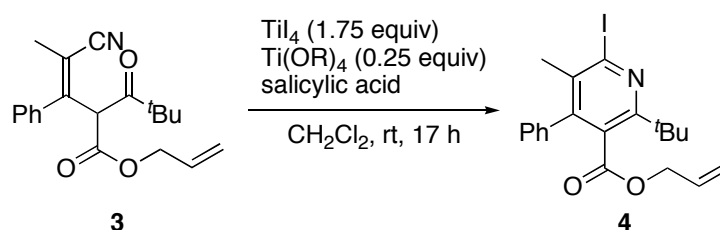


Scheme 1. 2-Iminopyrone (**2**) synthesis using the decarboxylation of β -keto ester (**1**) with NaCl



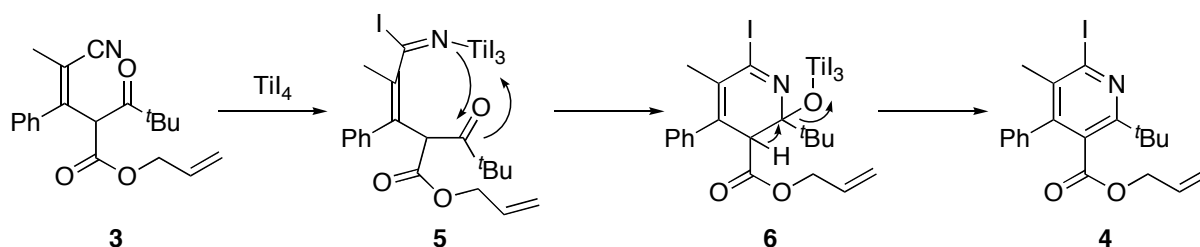
Scheme 2. 2-Iminopyrone (**2**) synthesis using the decarboxylation of β -keto allyl ester (**3**) with TiI_4

The present iodination-cyclization reaction most probably proceeds as shown in Scheme 3. The titanium intermediate (**5**) would be formed via a nucleophilic addition of iodide ion to cyano group. Subsequent intramolecular cyclization of this species (**5**) would give a titanium alkoxide intermediate (**6**), which would undergo aromatization via elimination of titanium oxide to give 2-iodopyridine (**4**).¹⁰

Table 1. Synthesis of 2-Iodopyridine (**4**)

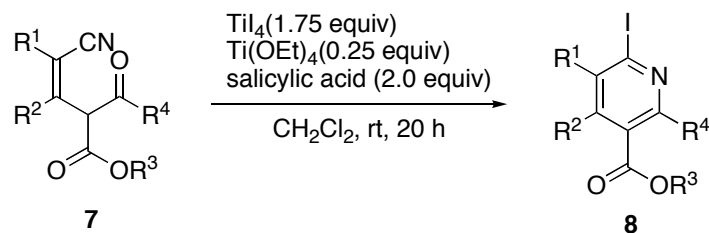
Entry	Ti(OR) ₄	Salicylic acid (equiv)	Yield (%) ^a
1 ^b	none	none	12 (52)
2	Ti(O ^{<i>i</i>} Pr) ₄	none	32 (45)
3	Ti(OMe) ₄	none	34 (42)
4	Ti(OEt) ₄	none	34 (48)
5	Ti(O ^{<i>n</i>} Bu) ₄	none	33 (45)
6	Ti[O(CH ₂) ₁₇ CH ₃] ₄	none	32 (48)
7	Ti(OEt) ₄	1.0	52 (20)
8	Ti(OEt) ₄	2.0	61

^a Isolated yield. Yields of the recovered cyano β-keto allyl ester (**3**) in parentheses. ^b The reaction was carried out using 1.7 equivalents of TiI₄ for 20 h.

**Scheme 3.** Plausible mechanism for the synthesis of 2-iodopyridine (**4**)

Several examples of the present 2-iodopyridine (**8**) synthesis were examined. Table 2 summarizes the results.¹¹ The reaction of β-*tert*-butyl keto esters (**7**) gave 2-iodopyridines (**8a**), (**8b**), and (**8c**) in moderate yields, respectively (entries 1-3), whereas the reaction of β-phenyl keto ester (**7d**) gave 2-iodopyridine (**8d**) in 25% yield (entry 4).

In conclusion, we have found a new synthetic route of multi-substituted 2-iodopyridines by the reaction of 2-(2-cyanoalk-1-enyl)-β-keto ester with TiI₄. The present method is an attractive synthetic route of multi-substituted 2-iodopyridines because 2-(2-cyanoalk-1-enyl)-β-keto esters are readily prepared as a cyclization precursor from cyanoacetate derivatives and alkynyl ketones, and furthermore, a 2-iodo substituent can be transformed into other functional groups such as alkoxy,¹² alkynyl,¹³ aryl,^{14,15} arylsulfanyl,¹⁵ or allyl¹⁵ groups.

Table 2. Synthesis of 2-Iodopyridine (**8**)

Entry	Cyano- β -keto ester	Product	Yield (%) ^a
1			47
2			47
3 ^b			36 (44) ^c
4			25

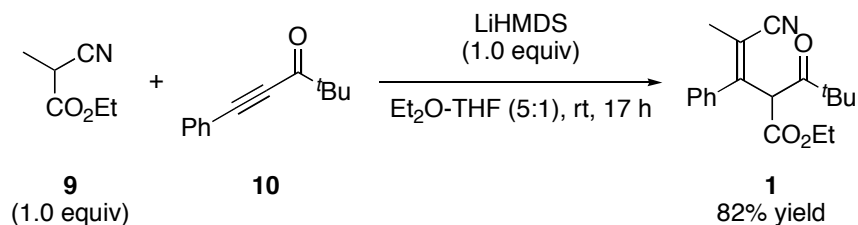
^a Isolated yield. ^b The reaction was carried out for 3 h. ^c Yield of the recovered starting material (**7c**) in parenthesis.

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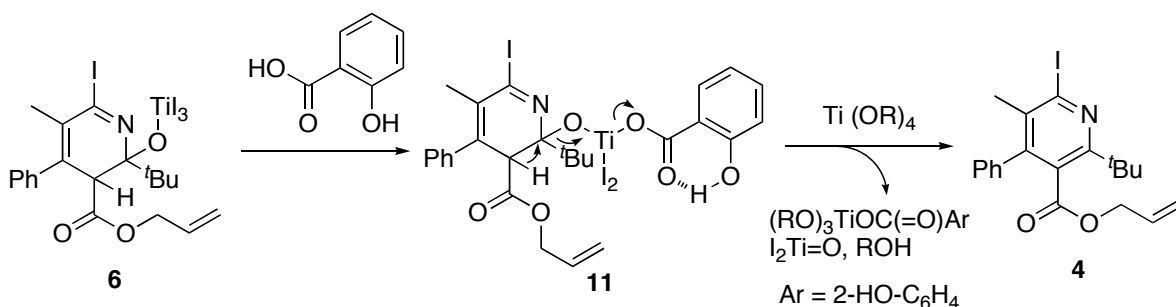
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4. 2-(2-Cyanoalk-1-enyl)- β -keto ester (**1**) was prepared from ethyl 2-cyanoacrylate (**9**) with alkynyl ketone (**10**) as shown in Scheme 4.



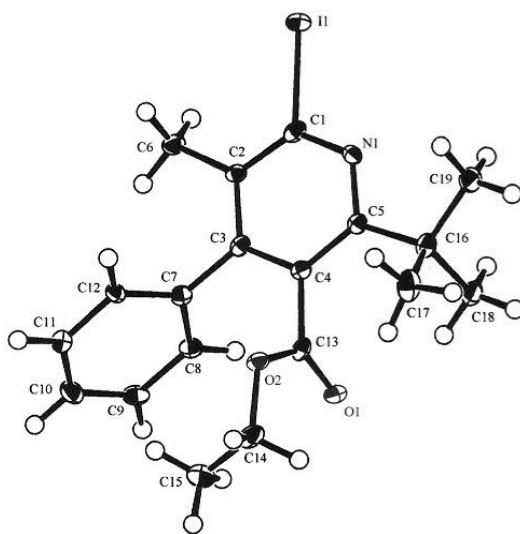
Scheme 4. Synthesis of 2-(2-cyanoalk-1-enyl)- β -keto ester (**1**)

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10. Although the roles of titanium tetraalkoxide and salicylic acid are not yet clear, we presume that a ligand exchange of titanium alkoxide intermediate (**6**) with salicylic acid would occur to generate titanium salicylate intermediate (**11**), which would undergo aromatization via elimination of titanium oxide by deprotonation with titanium tetraalkoxide as a base to give 2-iodopyridine (**4**) as shown in Scheme 5.



Scheme 5. The roles of titanium tetraalkoxide and salicylic acid

11. To a suspension of TiI_4 (194 mg, 0.35 mmol) in CH_2Cl_2 (0.5 mL) was added successively $\text{Ti}(\text{OEt})_4$ (0.050 mL, 0.050 mmol, 1.0 M in CH_2Cl_2) and a solution of **7c** (61.5 mg, 0.20 mmol) in CH_2Cl_2 (1.5 mL) at rt. The resulting mixture was stirred at rt for 3 h. The reaction was quenched with sat. aq. NaHCO_3 and 5% aq. NaHSO_3 . The mixture was filtrated through a Celite pad. The layers were separated and extracted with EtOAc (15 mL x 3). The combined organic extracts were washed with sat. aq. NaHCO_3 and brine, and then dried over anhydrous Na_2SO_4 . Purification on silica gel TLC (*n*-hexane/EtOAc = 10/1) gave the 2-iodopyridine (**8c**) (30.0 mg, 36% (65% conversion yield)) and the recovered β -keto ester (**7c**) (27.1 mg, 44%). **8c**: White solid. Mp 108.5-109.5 °C. ^1H NMR (500 MHz, CDCl_3): $\delta = 7.34\text{-}7.43$ (m, 3H), 7.11-7.15 (m, 2H), 3.80 (q, $J = 7.3$ Hz, 2H), 2.10 (s, 3H), 1.38 (s, 9H), 0.87 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3): $\delta = 168.6, 162.2, 147.8, 137.2, 133.7, 128.6, 128.1, 128.1, 125.6, 61.0, 39.2, 30.0, 24.1, 13.3$. IR (KBr): 3060, 2982, 2967, 2937, 1729, 1540, 1518, 1489, 1463, 1442, 1403, 1365, 1259, 1231, 1205, 1194, 1151, 1076, 1016, 948, 863, 752, 701, 639, 583 cm^{-1} . HRMS (EI): calcd. for $\text{C}_{19}\text{H}_{22}\text{INO}_2$ 423.0695 $[\text{M}]^+$; found 423.0703.



Scheme 6. ORTEP figure of 2-iodopyridine (**8c**)

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