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

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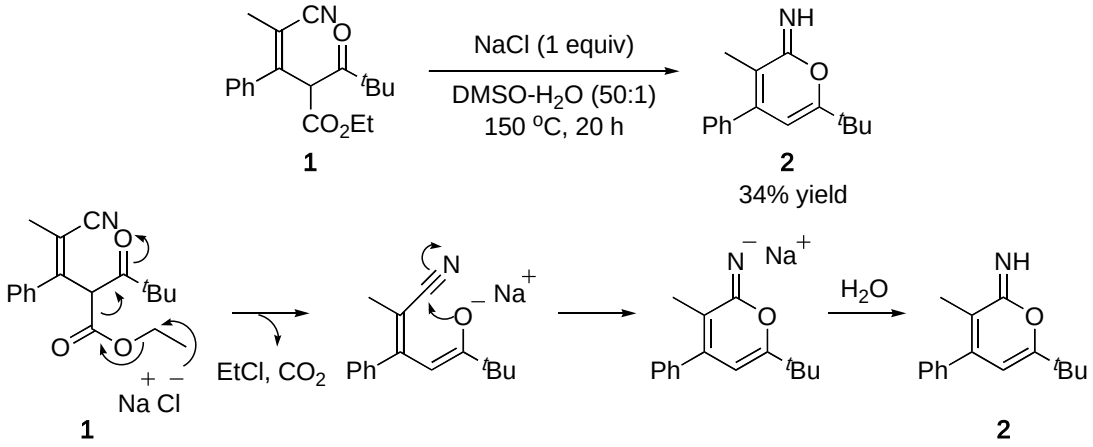
Abstract – Highly substituted 2-iodopyridines were synthesized from 2-(2-cyanoalk-1-enyl)-β-keto esters under the influence of titanium tetraiodide that worked efficiently for iodination-cyclization.

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 heterocyle formations using conjugate addition reactions to alkynyl imines[2] 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.

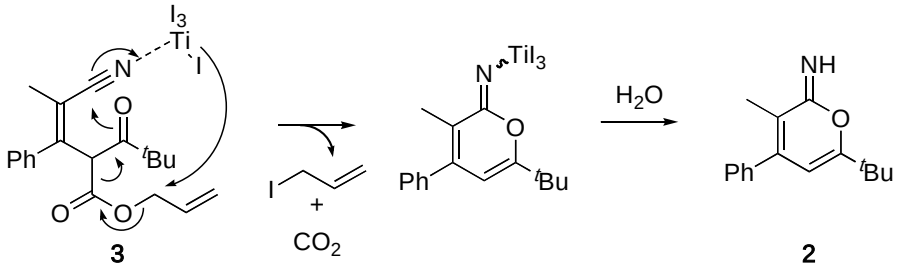
Regarding other nitrogen-containing heterocycles, we found that the decarboxylation-cyclization reaction of 2-(2-cyanoalk-1-enyl)-β-keto ester (**1**)[4] gave 2-iminopyrone (**2**) (Scheme 1). The decarboxylation was carried out in the presence of one equivalent of sodium chloride in DMSO-H_2O (50:1) at 150 ^oC 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 TiI_4 by a reaction mechanism as shown in Scheme 2.[6] The reaction of cyano-β-keto allyl ester (**3**) with TiI_4 (1.7 equiv) was carried out in CH_2Cl_2 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 $TiCl_4$

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 $Ti(O^iPr)_4$ 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 $Ti(OEt)_4$ (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 $Ti(OEt)_4$ (0.25 equiv) and salicylic acid (2.0 equiv) as additives gave 2-iodopyridine (**4**) in 61% yield (entry 8).



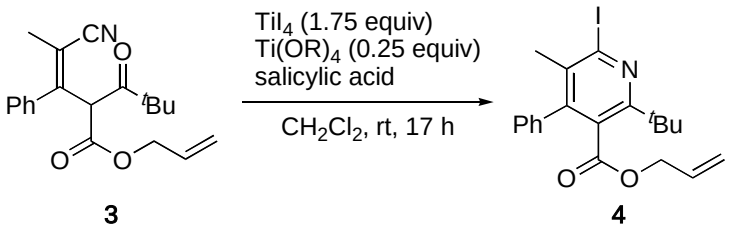
Scheme 1. 2-Iminopyrone (**2**) synthesis using the decarboxylation of β-keto ester (**1**) with NaCl



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]

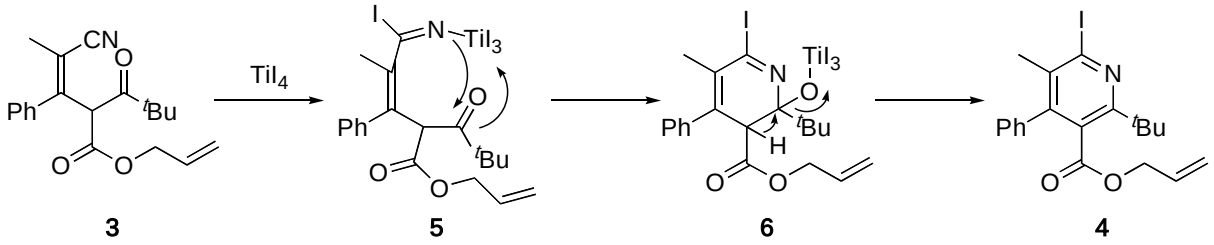
Table 1. Synthesis of 2-Iodopyridine (**4**)



3 **4**

Entry	$Ti(OR)_4$	Salicylic acid (equiv)	Yield (%)[a]
1[b]	none	none	12 (52)
2	$Ti(O^iPr)_4$	none	32 (45)
3	$Ti(OMe)_4$	none	34 (42)
4	$Ti(OEt)_4$	none	34 (48)
5	$Ti(O^nBu)_4$	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 TiI_4 for 20 h.



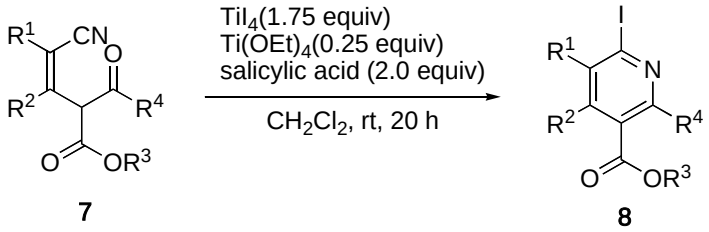
3 **5** **6** **4**

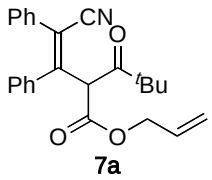
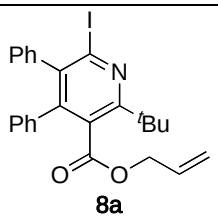
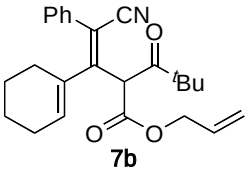
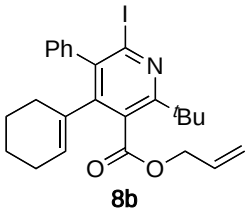
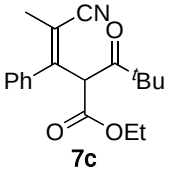
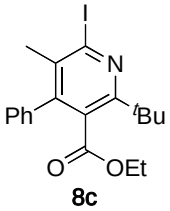
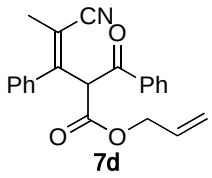
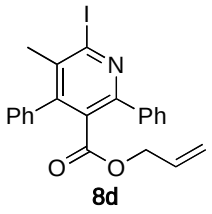
Scheme 3. Plausible mechanism for the synthesis of 2-iodopyridine (**4**)

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 TiI_4. 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 allyl[15] groups.

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



Entry	Cyano-β-keto ester	Product	Yield (%)[a]
1	 **7a**	 **8a**	47
2	 **7b**	 **8b**	47
3[b]	 **7c**	 **8c**	36 (44)[c]
4	 **7d**	 **8d**	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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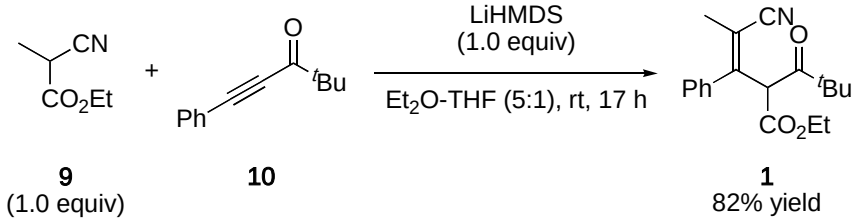
4. 2-(2-Cyanoalk-1-enyl)-β-keto ester (**1**) was prepared from ethyl 2-cyanopropanoate (**9**) with alkynyl ketone (**10**) as shown in Scheme 4.



9 (1.0 equiv) **10** **1** 82% yield

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

5. (a) A. P. Krapcho, *Synthesis*, 1982, 805. (b) A. P. Krapcho, *Synthesis*, 1982, 893.
6. Use of TiI_4 for iodination, see: (a) M. Shimizu, T. Toyoda, and T. Baba, *Synlett*, 2005, 2516. (b) M. Shimizu, T. Baba, S. Todou, and I. Hachiya, *Chem. Lett.*, 2007, **36**, 12, and references therein.
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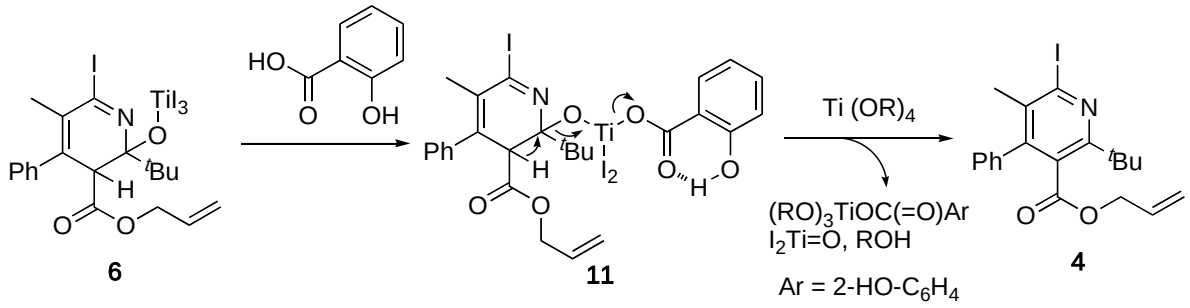
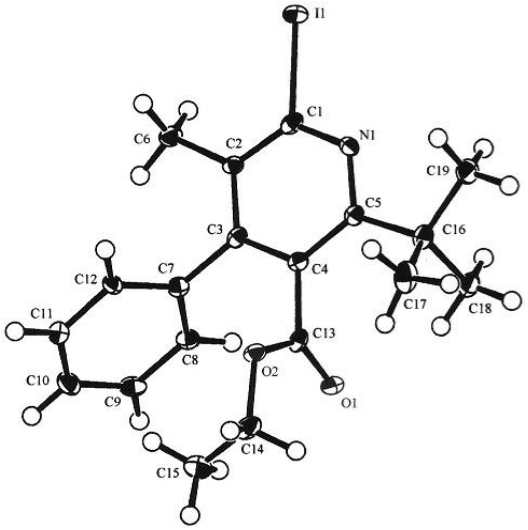
9. (a) R. Hayakawa and M. Shimizu, *Org. Lett.*, 2000, **2**, 4079. (b) M. Shimizu, M. Tanaka, T. Itoh, and I. Hachiya, *Synlett*, 2006, 1687.
10. Although the roles of titanium tetraalkoxide and salicylic acid are not yet clear, we presume that a ligand exchange of titanium alkoxide intermediate (**6**) 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 $Ti(OEt)_4$ (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. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34-7.43 (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, $CDCl_3$): δ = 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 $C_{19}H_{22}INO_2$ 423.0695 $[M]^+$; found 423.0703.



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

12. For recent examples of transformation into alkoxy groups, see: (a) R. A. Altman, A. Shafir, A. Choi, P. A. Lichtor, and S. L. Buchwald, *J. Org. Chem.*, 2008, **73**, 284. (b) P. W. Ondachi and D. L.

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13. For recent examples of transformation into alkynyl groups, see: (a) J. D. Crowley, D. A. Leigh, P. J. Lusby, R. T. McBurney, L.-E. Perret-Aebi, C. Petzold, A. M. Z. Slawin, and M. D. Symes, *J. Am. Chem. Soc.*, 2007, **129**, 15085. (b) C. Engtrakul and L. R. Sita, *Organometallics*, 2008, **27**, 927. (c) M. F. Martínez-Esperón, D. Rodríguez, L. Castedo, and C. Saá, *Tetrahedron*, 2008, **64**, 3674.
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15. For a recent example of transformation into arylsulfanyl or allyl groups, see: W. Lin, L. Chen, and P. Knochel, *Tetrahedron*, 2007, **63**, 2787.