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Intermolecular Reductive Cross Coupling of Carbonyl Compounds with Nitriles Induced by Low–valent Titanium

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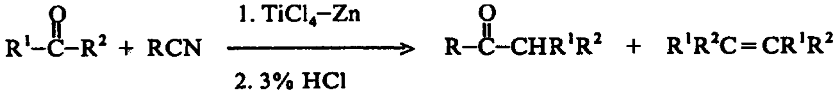
Abstract: Intermolecular cross coupling of carbonyl compounds with nitriles promoted by $TiCl_4$–Zn leads to ketones.

Carbonyl compounds undergo intermolecular reductive coupling reaction to yield olefins on treatment with low–valent titanium reagent.[1] The reaction is usually limited to the preparation of symmetrical olefins from ketones or aldehydes. The coupling reaction of two different carbonyl compounds can also be carried out in some cases.[2] However, the intermolecular reductive coupling of two compounds with different functional groups induced by low–valent titanium has not been reported in the literature. It could be expected that treatment of an active carbonyl compound together with a less active nitrile will lead to some amount of cross–coupling product. We now describe a novel method of synthesizing ketones via an intermolecular reductive cross coupling of aldehydes or ketones with nitriles induced by $TiCl_4$–Zn .

When an aldehyde(1) and a nitrile(2) were treated with low–valent titanium, the cross coupling product ketone(3) was obtained along with an olefin(4) the self reductive coupling product of the aldehyde. The similar outcome was also found in the cross coupling of nitriles with ketones.



$$R^1\!-\!\overset{O}{\overset{\|}{C}}\!-\!R^2 + RCN \xrightarrow[\text{2. 3\% HCl}]{\text{1. }TiCl_4\text{–Zn}} R\!-\!\overset{O}{\overset{\|}{C}}\!-\!CHR^1R^2 + R^1R^2C{=}CR^1R^2$$

1 2 3 4

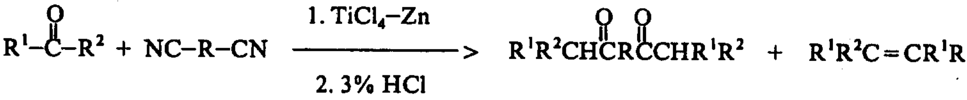
1		2	Isolated Yield(%)	
R^1	R^2	R	Ketone(3)	Olefin(4)
$4\text{–}ClC_6H_4$	H	$4\text{–}CH_3C_6H_4$	37.2	48.8
$4\text{–}CH_3C_6H_4$	H	C_6H_5	41.3	43.7
$4\text{–}CH_3C_6H_4$	H	$4\text{–}CH_3C_6H_4$	37.8	34.7
CH_3	CH_3CH_2	C_6H_5	37.0	
C_6H_5	C_6H_5	$CH_3(CH_2)_2$	62.3	16.5
C_6H_5	C_6H_5	C_6H_5	86.1	7.4
C_6H_5	C_6H_5	$4\text{–}ClC_6H_4$	72.7	12.6
C_6H_5	C_6H_5	$4\text{–}CH_3OC_6H_4$	79.2	16.6

Dedicated to Professor Tsiyu Kao on the occasion of his 90th birthday.

A general procedure is as follows: A dry 100mL flask was charged with Zinc dust (3.90 g, 60 mmol), $TiCl_4$ (3.30 mL, 30 mmol) and THF (50 mL). The mixture was refluxed for 2 h under Argon, then cooled to r.t.. During that time a black slurry was formed. A mixed solution of a nitrile (10 mmol) and a carbonyl compound (10 mmol) in THF (10 mL) was added to the reaction mixture over 3 h using a syringe, stirred for another 3 h at r.t, then refluxed for 40h. After removing the THF, the mixture was quenched with 3% HCl (250 mL) and extracted with $CHCl_3$(3x50 mL). The combined organic layer was washed with saturated NaCl (50 mL), dried(Na_2SO_4) and evaporated. The crude product was purified by recrystallization in ethanol or by chromatography on silica gel (dichloromethane / petroleum ether(60–90℃), 1: 3) to give ketone and olefin. All new compounds were completely characterized by elemental and spectroscopic analysis.

The experimental results given below show that: when nitriles reacted with aldehydes, the major products were olefins(4) from the self coupling of the aldehyde; while the reaction between nitriles and ketones mainly gave the cross coupling products(3). It is considered that the low–valent titanium reagent could reduce carbonyl group first to form corresponding ketyl radical which in turn reacted with nitrile or another carbonyl compound to form the cross–coupling compound or the self–coupling compound and it is worth mentioning that aromatic aldehydes or ketones gave more satisfactory yields.

We could also obtain diketones(6) from dinitriles(5) and two equivalents of aromatic ketones(1) with much higher yields.

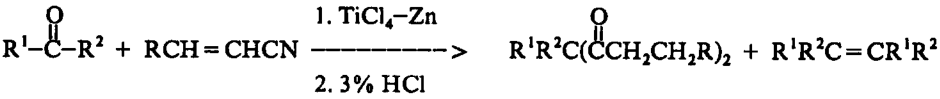


$$R^1-\overset{O}{\overset{\|}{C}}-R^2 + NC-R-CN \xrightarrow[2.\ 3\%\ HCl]{1.\ TiCl_4-Zn} R^1R^2CH\overset{O}{\overset{\|}{C}}R\overset{O}{\overset{\|}{C}}CHR^1R^2 + R^1R^2C=CR^1R^2$$

1 5 6 4

1		5	Isolated Yield(%)	
R¹	R²	R	Ketone(6)	Olefin(4)
C_6H_5	C_6H_5	$(CH_2)_4$	67.5	24.3
C_6H_5	4–ClC_6H_4	1, 4–C_6H_4	71.2	18.1

Two equivalents of unsaturated nitriles(7) and one equivalent of aromatic ketones(1) provided β–diketones(8).

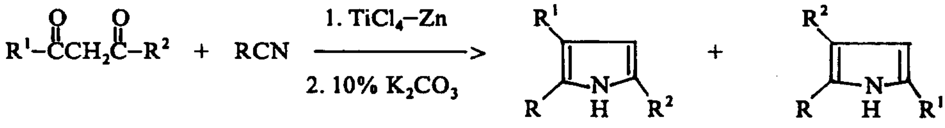


$$R^1-\overset{O}{\overset{\|}{C}}-R^2 + RCH=CHCN \xrightarrow[2.\ 3\%\ HCl]{1.\ TiCl_4-Zn} R^1R^2C(\overset{O}{\overset{\|}{C}}CH_2CH_2R)_2 + R^1R^2C=CR^1R^2$$

1 7 8 4

1		7	Isolated Yield(%)	
R¹	R²	R	Ketone(8)	Olefin(4)
C_6H_5	C_6H_5	C_6H_5	42.3	47.8
C_6H_5	C_6H_5	$4\text{-}CH_3OC_6H_4$	22.4	58.2

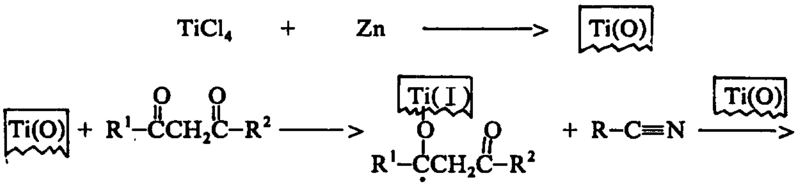
Attempts to induce the cross coupling between nitriles and diketones were unsuccessful and gave only cycloalkenes[3] which are the intramolecular coupling products of the diketones. Ketones are far more active than nitriles and intramolecular reaction could occur much easier than intermolecular one. An exception is the case of β–diketones, we got pyrrole(10) by treating nitrile(2) with β–diketone(9).[4] The great steric strain for the intramolecular cyclization of the β–diketones is probably the reason why the coupling reaction is driven to take an intermolecular way.

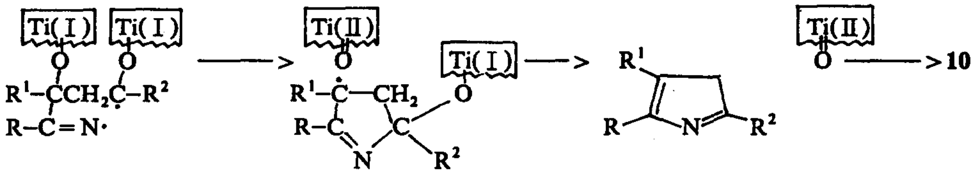


9 2 10A 10B

9		2		Yield(%)
R¹	R²	R	10A	10B
C_6H_5	C_6H_5	C_6H_5		86.9
C_6H_5	C_6H_5	$4\text{-}ClC_6H_4CH_2$		69.8
C_6H_5	CH_3	C_6H_5	7.1	28.5

The mechanism of this reaction may be postulated as Scheme I.





Scheme I

In the initial step, an electron is transferred from titanium to the carbonyl group generating a radical anion[5], the ketyl radical then attacks the nitrile to from the carbon–carbon bond and an imino–nitrogen radical, the latter then couples with the ketyl radical derived from second carbonyl group to give the carbon–nitrogen bond. After deoxygenation and tautomerization, pyrrole(**10**) is formed.

Acknowledgement

We thank National Nature Science Fundation of China for generous support of this project.

References and Notes:

[1] J. E. McMurry Chem. Rev. 1989, 89, 1513.

[2] J. E. McMurry, L. R. Krepski J. Org. Chem. 1976, 41, 3929. S. M. Reddy, M. Duraisamy, H. M. Walborsky J. Org. Chem. 1986, 51, 2361.

[3] In this condition, we obtain 1,2–dimethylcyclohexene, and 1,2–diphenylcyclohexene from the intramolecular coupling of 2,7–octadione and 1,6–diphenyl–1,6–hexadione. J. E. McMurry, M. P. Fleming, K. L. Kess, L. R. Krepski J. Org. Chem. 1978, 43, 3255.

[4] Using 10% aqueous K_2CO_3 to quench the reaction mixture is the only difference from the general procedure.

[5] R. Dams, M. Malinowski, I. Westdorp, H. J. Geise J. Org. Chem. 1982, 47, 248.

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