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Titanium isopropoxide/pyridine mediated Knoevenagel reactions

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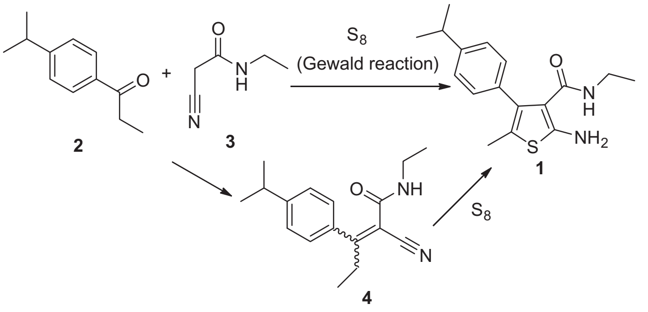
ABSTRACT

We report a Ti(O*i*Pr)$_4$/pyridine mediated Knoevenagel reaction between aromatic ketones and cyanoacetamides to provide Knoevenagel olefin products in good to excellent yields. Almost in all cases studied, a single geometrical isomer was formed and isolated under the Ti(O*i*Pr)$_4$/pyridine condensation conditions. This methodology was also demonstrated to be highly effective between some other Knoevenagel active methylene compounds and aromatic ketones.

Recently, as part of our medicinal chemistry efforts in developing therapeutic agents for central nervous system (CNS) diseases, we desired the multifunctionalized 2-aminothiophene **1** (Scheme 1) as a key intermediate to synthesize derivatives for structure–activity relationship (SAR) studies. The classical synthesis for 2-aminothiophenes is through Gewald reaction which typically involves a ketone or aldehyde, a methylene active nitrile, elemental sulfur, and an amine.[1,2] However, in the case of **1**, this classical reaction provided essentially no product under a variety of reaction conditions. Upon close examination, we found that the olefin **4**, which is the presumed intermediate for the Gewald product **1**, was not formed under the reaction conditions. An efficient two-step synthesis for aminothiophene **1** through olefin **4** was desired and is the subject of this report.

The Knoevenagel reaction was discovered more than a century ago and covers a variety of condensations typically between an aldehyde or a ketone and an active methylene compound in the presence of a weak base to provide olefin derivatives.[3,4] While the reaction in general works well with aldehydes, ketones, especially aromatic ketones, which are much less reactive do not condense well. It was not surprising that condensation between **2** and **3** under standard Knoevenagel reaction conditions did not proceed (entries 1 and 2, Table 1). Much to our disappointment, the Lehnert modification (TiCl$_4$/base)[5,6] which has been successfully used for certain ketones and less reactive aldehydes also failed in this case (entry 3, Table 1). Ti(O*i*Pr)$_4$ is a good Lewis acid and an excellent dehydrating agent and has been used liberally for a variety of otherwise challenging condensations such as formations of urea imines[7] and sulfinimines.[8] To the best of our knowledge, this reagent has not been well studied for Knoevenagel reactions. The only report about Ti(O*i*Pr)$_4$ in context of the Knoevenagel reaction is its catalyzed reactions between malononitrile and several aldehydes.[9] This prompted us to investigate its utility in the Knoevenagel reaction, specifically those with challenging starting components.

Condensation of **2** and **3** with 1 equiv of Ti(O*i*Pr)$_4$ and 1 equiv of pyridine in THF at room temperature (rt) for 15 h provided the desired product **4** with 36% conversion as determined by LC–MS (entry 4, Table 1). The conversion improved dramatically with additional equivalents of Ti(O*i*Pr)$_4$ (entries 5 and 6, Table 1). In the absence of pyridine (entry 8, Table 1) the reaction was significantly slower indicating that pyridine plays an important role in promoting the condensation. The optimal conditions identified



Scheme 1. Geward and 2-step synthesis of thiophenes.

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Table 1
Condensations between **2** and **3**

Entry	Reaction conditions[a]	Conversion %[b]
1	$NH_4OAc/HOAc$	0
2	Morpholine/HOAc	0
3	$TiCl_4$/pyridine	0
4	1 equiv Ti(O*i*Pr)$_4$, 1 equiv pyridine	36
5	2 equiv Ti(O*i*Pr)$_4$, 1 equiv pyridine	64
6	3 equiv Ti(O*i*Pr)$_4$, 2 equiv pyridine	89
7	3 equiv Ti(O*i*Pr)$_4$, 3 equiv pyridine	72
8	3 equiv Ti(O*i*Pr)$_4$, 0 equiv pyridine	50
9	3 equiv Ti(OEt)$_4$, 2 equiv pyridine	37
10	3 equiv Ti(OPr)$_4$, 2 equiv pyridine	38

[a] All Ti(OR)$_4$ mediated reactions were carried out at rt for 15 h.
[b] Conversion was determined using LC–MS with an internal standard.

are 3 equiv of Ti(O*i*Pr)$_4$ and 2 equiv of pyridine. The reason for the lower conversion with more than 2 equiv of pyridine is not clear. Other bases such as Et_3N and *N*-methyl morpholine were also explored and it was found that pyridine is the optimal choice. Among several solvents examined, CH_2Cl_2 was less effective, but Et_2O and toluene provided comparable results to that of THF. A number of other titanium alkoxides including Ti(OEt)$_4$ and Ti(OPr)$_4$ were also tested and were found to be less effective than Ti(O*i*Pr)$_4$ (entries 9 and 10, Table 1).

Under the optimal reaction conditions, condensation of **2** and **3** provided the desired product in 83% isolated yield (**7a**, Table 2). Interestingly, only one geometrical isomer was formed (as determined by LC–MS) and isolated with configuration being *Z* as determined by 2-D NMR (ROESY). To further explore the scope and

Table 2
Ti(O*i*Pr)$_4$/pyridine mediated Knoevenagel reactions[a]

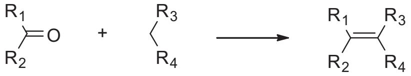
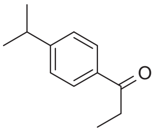
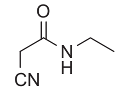
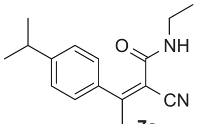
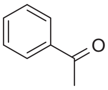
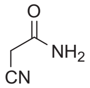
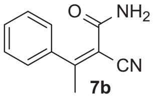
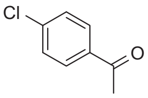
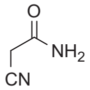
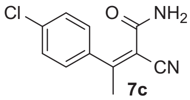
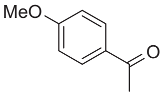
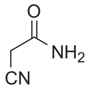
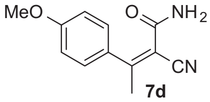
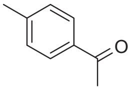
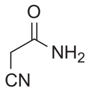
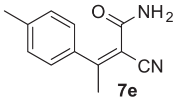
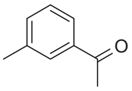
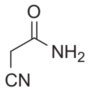
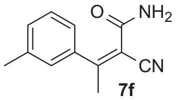
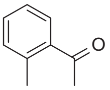
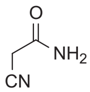
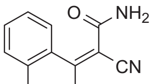
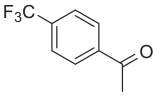
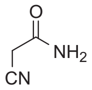
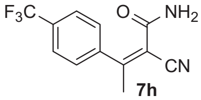
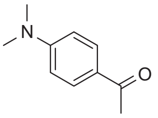
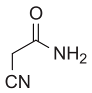
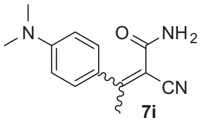
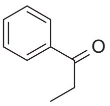
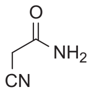
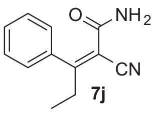
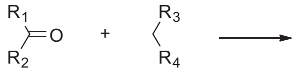
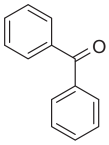
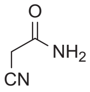
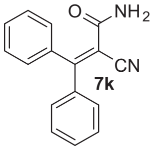
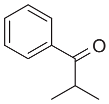
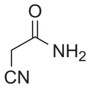
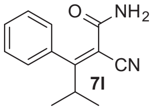
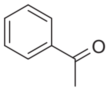
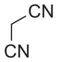
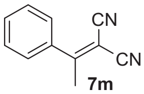
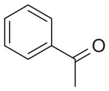
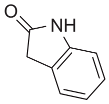
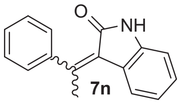
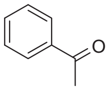
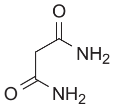
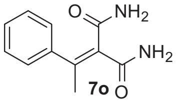
 **5**	**6**	**7**	Yield %[b]	Configuration
		 **7a**	83	Single isomer (*Z*)
		 **7b**	93	Single isomer (*Z*)
		 **7c**	95	Single isomer (*Z*)
		 **7d**	88	Single isomer (*Z*)
		 **7e**	82	Single isomer (*Z*)
		 **7f**	82	Single isomer (*Z*)
		 **7g**	71	Single isomer (*Z*)
		 **7h**	72	Single isomer (*Z*)
		 **7i**	78	~50:50 (*Z*/*E*)
		 **7j**	88	Single isomer (*Z*)

Table 2 (*continued*)

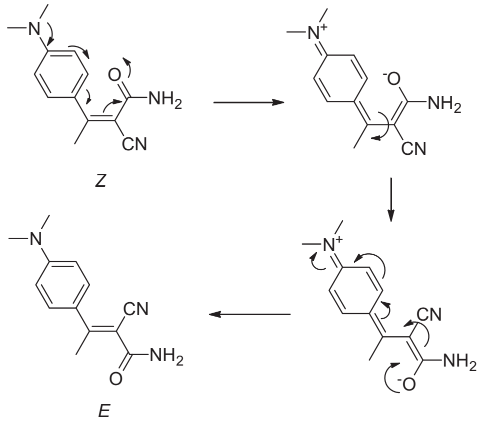
 5 6 7			Yield %[b]	Configuration
		 7k	65	–
		 7l	56[c]	Single isomer (*Z*)
		 7m	90	–
		 7n	92	~90:10 (*Z*/*E*)
		 7o	0	–

[a] Reaction conditions: 3 equiv Ti(O*i*Pr)$_4$, 2 equiv pyridine, THF, rt, overnight (typically 15 h).

[b] Isolated yield.

[c] 60 °C, 72 h.

limitation of this methodology, commercially available cyanoacetamide was chosen to condense with a number of aromatic ketones and the data is summarized in Table 2. Substitutions with both electron-withdrawing and electron-donating groups (**7a–i**) on the aromatic ring were well-tolerated and good to excellent yields were obtained. The reaction, however, is quite sensitive to steric effects. Moderate yield was obtained for the benzophenone substrate (**7k**, Table 2) when the reaction was carried out at rt. In the case of isopropyl phenyl ketone (**7l**), the reaction was very sluggish at rt and only proceeded with prolonged heating (60 °C, 72 h). The efficiency of the reaction can potentially be further improved with microwave heating. Like 4-isopropyl ethyl ketone (**2**), all other unsymmetric ketones, with one exception, also provided single *Z* isomers which were isolated without any isomerization. The exception is **7i**, which was formed as a single geometrical isomer but subsequently isomerized during the chromatographic purification.[10] The isomerization was presumably facilitated by the *N,N*-dimethylamino group through a proposed mechanism shown in Scheme 2.



Scheme 2. Proposed mechanism for isomerization of **7i**.

A few active methylene compounds were then chosen to condense with acetophenone in order to further determine the scope and limitation of this Ti(O*i*Pr)$_4$/pyridine mediated Knoevenagel condensation (7**m–o**). While excellent yields were obtained for **7m** and **7n**, no desired product of **7o** formed even at elevated temperatures (60 °C, 72 h).

To complete the assembly of the thiophene derivative, the reaction between **4** and elemental sulfur was executed smoothly to provide 2-aminothiophene **1** (Scheme 1). The successful preparation of this compound serves as an example of the utility of the Ti(O*i*Pr)$_4$/pyridine mediated Knoevenagel condensation methodology.

Typical procedure of Ti(OiPr)$_4$/pyridine mediated Knoevenagel condensations (**7a**): A mixture of 1-(4-isopropylphenyl)propan-1-one (4.12 g, 23.4 mmol), 2-cyano-*N*-ethylacetamide (2.62 g, 23.4 mmol), and pyridine (3.70 g, 46.7 mmol) in THF (40 mL) was stirred for 10 min followed by addition of titanium isopropoxide (19.9 g, 70.1 mmol). The resulting mixture was stirred at rt for 15 h. LC–MS showed that majority of the starting material was converted to the product. The reaction mixture was diluted with EtOAc and washed with 1 N aqueous HCl, NaHCO$_3$, and brine. The organic layer was dried over Na$_2$SO$_4$, concentrated, and purified by chromatography with 10–80% EtOAc in hexanes to provide (*Z*)-2-cyano-*N*-ethyl-3-(4-isopropylphenyl)pent-2-enamide (5.24 g, 82.9%).

In summary, we have developed a Ti(O*i*Pr)$_4$/pyridine mediated Knoevenagel condensation between aromatic ketones and cyanoacetamides to provide Knoevenagel olefin products in good to excellent yields. Almost in all cases studied, a single geometrical isomer was formed and isolated under the Ti(O*i*Pr)$_4$/pyridine condensation conditions. This methodology was also demonstrated to be highly effective between some other Knoevenagel active methylene compounds and aromatic ketones, particularly those that are not effective under typical Knoevenagel condensation conditions.

Acknowledgments

We acknowledge Herik Pedersen and Qing Ping Han for their analytical supports.

Supplementary data

Supplementary data (general procedures) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.069.

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10. Unlike all other reactions which were worked up by washing with 1 N HCl, this reaction was washed with only water due to the basicity of *N*,*N*-dimethylamino group. No isomerization occurred during this workup.