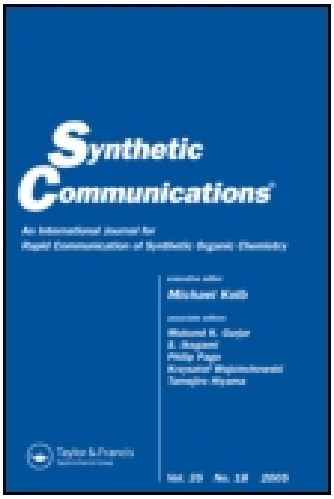

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Rapid, Highly Efficient, and Room-Temperature $TiCl_4$-Catalyzed Synthesis of Δ^4-Isoxazolines Under Solvent-Free Conditions

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RAPID, HIGHLY EFFICIENT, AND ROOM-TEMPERATURE $TiCl_4$-CATALYZED SYNTHESIS OF Δ^4-ISOXAZOLINES UNDER SOLVENT-FREE CONDITIONS

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Δ⁴-Isoxazoline derivatives were synthesized in excellent yields via the titanium tetrachloride–catalyzed 1,3-dipolar cycloaddition reaction of nitrones with α,β-unsaturated compounds under neat conditions at room temperatures in very short reaction time.

Keywords: Cycloadditions; isoxazoline; nitrone; solvent-free; titanium tetrachloride

INTRODUCTION

Isoxazoline moieties and isoxazolidines[1,2] possess a wide spectrum of activities such as antifungal, anticancer, antiviral, insecticidal, and antibiotic activities and are precursors for different natural products.[3] One of the most common procedures for the synthesis of these compounds is cycloaddition reaction of 1,3-dipoles to olefins. The 1,3-dipolar cycloaddition, also known as the Huisgen cycloaddition, is a well-known reaction in organic chemistry consisting of the reaction of alkenes or alkynes with 1,3-dipolar compounds to synthesize various heterocycles such as isoxazolines.[4] A range of different substituents can be included in the dipole and the dipolarophile, resulting in a broad range of possible cycloadducts, which serve as useful synthetic building blocks. These reactions are synthetically very useful because of their high stereospecificity and stereoselectivity.[5–7] Several studies have reported on the effect of Lewis acid catalysts in these reactions.[8–10] The coordination of a Lewis acid to dipole or dipolarophile is of fundamental importance for asymmetric 1,3-dipolar cycloadditions, because the metal can catalyze the reaction. Regio- and stereoselectivity of these reactions can be controlled by the metal–ligand complexes.[11,12] According to many published reports, $TiCl_4$ has been used as a Lewis acid catalyst for the broad range of reactions such as converting the acetals to the corresponding carbonyl compounds,[13] activating the addition of carbon nucleophiles to acetals,[14–18] and reducing carboxylic esters to ethers.[19] Recently, we

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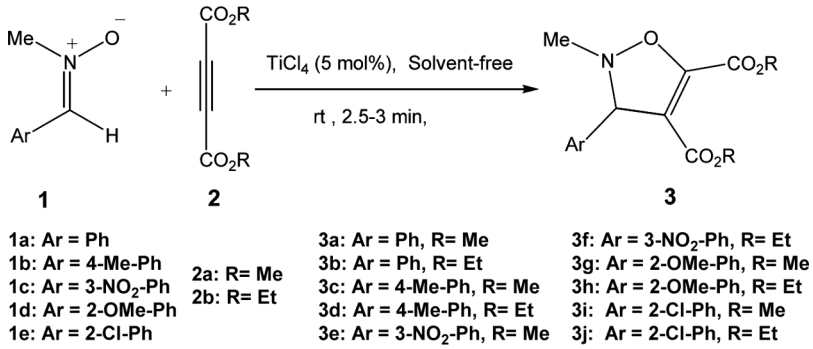

Scheme 1. $TiCl_4$-catalyzed synthesis of isoxazolines in solventless system.

reported the efficient synthesis of coumaris via the $TiCl_4$-catalyzed Pechmann condensation of phenols with β-ketoesters.[20]

Nitrone 1,3-dipoles have been used for the synthesis of isoxazoline derivatives in 1,3-dipolar cycloaddition reactions.[21–29] Despite the other 1,3-dipoles, nitrones are stable compounds and do not require in situ formation. To the best of our knowledge, no report has been made about the use of $TiCl_4$ catalyst for 1,3-dipolar cycloaddition of nitrones for the synthesis of isoxazole derivatives. In this report, we highlight our results on cycloaddition reactions of nitrones **1a–e** with dimethyl acethylenedicarboxylate (DMAD) **2a** and diethyl acethylenedicarboxylate (DEAD) **2b** in the presence of $TiCl_4$ to produce related isoxazoline derivatives in excellent yields in a solventless system (Scheme 1).

RESULTS AND DISCUSSION

For the beginning of this study, benzaldonitrone and DMAD were employed as the model reactants at room temperature in the presence of $TiCl_4$ to compare the catalytic performance of the $TiCl_4$. As shown in Table 1, <15% yield of Δ^4-isoxazoline **3a** could be detected by gas chromatography (GC) in the absence of $TiCl_4$ (entry 1), which indicated that the catalyst should be very effective for the reaction.

Table 1. Results of using different amounts of $TiCl_4$ and HCl on yields of isoxazolin **3a**[a]

Entry	Catalyst	Catalyst amount (mol%)[b]	Time (min)	Yield[c] (%)
1	$TiCl_4$	0	25	<15
2	$TiCl_4$	1	5	86
3	$TiCl_4$	5	3	92
4	$TiCl_4$	10	6	85
5	HCl	1	25	22
6	HCl	5	25	25
7	HCl	10	25	20

[a]15 mmol nitrone with 15 mmol DMAD.
[b]Molar ratio of catalyst to nitrone.
[c]Isolated yields by flash chromatography for entries 2–7 and by GC for entry 1.

Table 2. $TiCl_4$-catalyzed room-temperature synthesis of Δ^4-isoxazolines[a]

Entry	Olefin	Nitrone	Product	Time (min)	Yield (%)[b]
1	DMAD	**1a**	**3a**	3 min	92
2	DEAD	**1a**	**3b**	2.5 min	88
3	DMAD	**1b**	**3c**	2.5 min	93
4	DEAD	**1b**	**3d**	3 min	87
5	DMAD	**1c**	**3e**	3 min	91
6	DEAD	**1c**	**3f**	2.5 min	92
7	DMAD	**1d**	**3g**	3 min	94
8	DEAD	**1d**	**3h**	2.5 min	94
9	DMAD	**1e**	**3i**	3 min	96
10	DEAD	**1e**	**3j**	3 min	93

[a]15 mmol nitrone with 15 mmol DMAD.
[b]Isolated yields after flash chromatography for entries 1–10 and by GC for entries 11 and 12.

Various amounts of catalyst (1, 5, and 10 mol%) have been used for the model reaction. The results in Table 1 show that the optimum amount of catalyst was 5 mol%. Titanium tetrachloride is known to release hydrochloric acid (HCl). This prompted us to investigate the possibility of HCl acting as a catalyst in this procedure. We examined the reaction using various amounts of HCl as a catalyst and found that the reaction did not proceed smoothly in these conditions (entries 5–7).

Having optimized the reaction conditions, several Δ^4-isoxazolines were successfully synthesized (Table 2) in good yields by following this method. The reaction mixture was stirred at room temperature. We carried out these reactions with a series of nitrones with alkynes to obtain the corresponding five-membered heterocycles. In all cases, the reactions were completed within 2.5–3 min of reaction time. In the majority of the entries, the isoxazolines were formed fast and with final yields ranging from good to excellent (Table 2). We conducted these reactions on a 30-mmol scale and found smooth transformation to the isoxazoline derivatives in good yields. Thus, the present procedure is amenable for scaling up.

EXPERIMENTAL

General Information

All reagents were purchased from Merck Company and used without further purification. Infrared (IR) spectra were recorded in KBr and were determined on a Perkin-Elmer Fourier transform (FT)–IR spectrometer. ^{1}H NMR spectra were obtained in $CDCl_3$ solution from Bruker Avance AC 400-MHz instrument, and ^{13}C NMR spectra were measured at 100 MHz on the aforementioned instruments. Elemental analyses were carried out on a Perkin-Elmer 240C elemental analyzer and are reported in percentage of atomic abundance. Analytical thin-layer chromatography (TLC) was performed using precoated silica-gel 60 F254 plates (Merck, Darmstadt), and the spots were visualized with ultraviolet (UV) light at 254 nm. Merck silica gel 60 (230–400 mesh) was used for flash chromatography.

Synthesis of Δ^4-Isoxasolines, General Procedure

$TiCl_4$ (0.75 mmol) was added to a mixture of nitrone (15 mmol) and dipolarophile (15 mmol) in a 10-ml conical flask, and the mixture was shaken for a period of time at room temperature (TLC) as listed in Table 2. After completion of the reaction, 10 ml of an aqueous sodium bicarbonate solution was added and stirred for 2–5 min. The reaction mixture was extracted three times with 7 ml of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and evaporated under reduced pressure. Then the crude mixture was purified by flash chromatography on silica gel to afford the corresponding cycloadduct (Table 2).

Selected Spectral Data for Δ^4-Isoxazolines

2-Methyl-3-phenyl-4,5-dicarbomethoxy-Δ^4-isoxazoline (3a, $C_{14}H_{15}NO_5$). White crystals; mp 64.9–65.6 °C; IR (KBr): 1753, 1716, 1654, 1116 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$–7.25 (m, 5H, ArH), 5.00 (s, 1H, CH), 3.89 (s, 3H, Me), 3.61 (s, 3H, Me), 2.95 (s, 3H, Me). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 33.95$, 52.40, 50.72, 87.98, 111.64, 119.72, 125.32, 127.63, 129.56, 134.33, 159.58, 162.71. Anal. calcd. (%) for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found (%): C, 60.87; H, 5.37; N, 4.90.

2-Methyl-3-phenyl-4,5-dicarboethoxy-Δ^4-isoxazoline (3b, $C_{16}H_{19}NO_5$). Colorless liquid; IR (KBr): 1750, 1717, 1649, 1120 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$–7.23 (m, 5H, ArH), 5.09 (s, 1H, CH), 4.14 (q, $J = 7.19$ Hz, 2H, OCH_2CH_3), 4.10 (q, $J = 7.25$ Hz, 2H, OCH_2CH_3), 3.07 (s, 3H, NMe), 1.27 (t, $J = 7.19$ Hz, 3H, OCH_2CH_3), 1.23 (t, $J = 7.25$ Hz, 3H, OCH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 17.41$, 17.42, 35.51, 58.40, 58.96, 90.19, 113.16, 119.62, 125.11, 126.24, 129.89, 133.13, 160.50, 162.11. Anal. calcd. (%) for $C_{16}H_{19}NO_5$: C, 62.64; H, 6.27; N, 4.59. Found (%): C, 62.98; H, 6.03; N, 4.40.

2-Methyl-3-(4-methylphenyl)-4,5-dicarbomethoxy-Δ^4-isoxazoline (3c, $C_{15}H_{17}NO_5$). White crystals; mp 50–51 °C; IR (KBr): 1750, 1711, 1648, 1110 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.31$–7.25 (m, 4H, ArH), 5.11 (s, 1H, CH), 3.88 (s, 3H, Me), 3.69 (s, 3H, Me), 3.05 (s, 3H, Me), 2.38 (s, 3H, Me). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 24.12$, 33.95, 52.40, 50.72, 87.98, 111.64, 119.72, 124.44, 126.36, 129.96, 135.55, 159.58, 162.71. Anal. calcd. (%) for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found (%): C, 62.02; H, 5.67; N, 4.62.

2-Methyl-3-(4-methylphenyl)-4,5-dicarboethoxy-Δ^4-isoxazoline (3d, $C_{17}H_{21}NO_5$). Colorless liquid; IR (KBr): 1759, 1723, 1649, 1121 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.29$–7.20 (m, 4H, ArH), 5.02 (s, 1H, CH), 4.20 (q, $J = 7.16$ Hz, 2H, OCH_2CH_3), 4.13 (q, $J = 7.23$ Hz, 2H, OCH_2CH_3), 3.13 (s, 3H, NMe), 2.40 (s, 3H, Me), 1.29 (t, $J = 7.16$ Hz, 3H, OCH_2CH_3), 1.25 (t, $J = 7.23$ Hz, 3H, OCH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 18.40$, 18.52, 23.10, 36.50, 58.40, 58.91, 92.07, 112.17, 119.60, 124.11, 126.64, 129.80, 133.22, 161.01, 162.14. Anal. calcd. (%) for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found (%): C, 64.08; H, 6.49; N, 4.19.

2-Methyl-3-(3-nitrophenyl)-4,5-dicarbomethoxy-Δ^4-isoxazoline (3e, $C_{14}H_{14}N_2O_7$). White crystals; mp 78–79 °C; IR (KBr): 1752, 1709, 1638, 1535,

1356, 1120 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.21–7.05$ (m, 4H, ArH), 4.95 (s, 1H, CH), 3.80 (s, 3H, Me), 3.61 (s, 3H, Me), 3.05 (s, 3H, Me). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 32.95$, 51.43, 50.32, 86.18, 113.64, 120.12, 121.26, 123.98, 125.65, 127.87, 128.90, 133.33, 160.18, 164.11. Anal. calcd. (%) for $C_{14}H_{14}N_2O_7$: C, 52.18; H, 4.38; N, 8.69. Found (%): C, 52.25; H, 4.23; N, 8.50.

2-Methyl-3-(3-nitrophenyl)-4,5-dicarboethoxy-Δ^4-isoxazoline (3f, $C_{16}H_{18}N_2O_7$). Colorless liquid; IR (KBr): 1742, 1719, 1628, 1521, 1351, 1121 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.19–7.00$ (m, 4H, ArH), 4.96 (s, 1H, CH), 4.12 (q, $J = 7.06$ Hz, 2H, OCH_2CH_3), 4.03 (q, $J = 6.98$ Hz, 2H, OCH_2CH_3), 3.10 (s, 3H, NMe), 1.31 (t, $J = 7.06$ Hz, 3H, OCH_2CH_3), 1.21 (t, $J = 6.98$ Hz, 3H, OCH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 19.14$, 20.32, 37.59, 58.48, 59.90, 95.17, 114.09, 120.99, 123.36, 124.99, 125.68, 126.94, 130.09, 136.00, 164.09, 165.14. Anal. calcd. (%) for $C_{16}H_{18}N_2O_7$: C, 54.86; H, 5.18; N, 8.00. Found (%): C, 54.90; H, 5.03; N, 7.78.

2-Methyl-3-(2-methoxyphenyl)-4,5-dicarbomethoxy-Δ^4-isoxazoline (3g, $C_{15}H_{17}NO_6$). White crystals; mp 78.7–79.8 °C; IR (KBr): 1745, 1709, 1650, 1119 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.38–7.29$ (m, 4H, ArH), 5.12 (s, 1H, CH), 4.10 (s, 3H, OMe), 3.79 (s, 3H, Me), 3.66 (s, 3H, Me), 3.00 (s, H, Me). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 33.95$, 50.90, 51.35, 51.89, 88.18, 111.14, 117.84, 118.02, 121.70, 126.65, 128.09, 130.53, 136.09, 158.50, 165.01. Anal. calcd. (%) for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found (%): C, 58.72; H, 5.43; N, 4.41.

2-Methyl-3-(2-methoxyphenyl)-4,5-dicarboethoxy-Δ^4-isoxazoline (3h, $C_{17}H_{21}NO_6$). Colorless liquid; IR (KBr): 1749, 1720, 1650, 1115 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.38–7.27$ (m, 4H, ArH), 5.20 (s, 1H, CH), 4.21 (q, $J = 7.16$ Hz, 2H, OCH_2CH_3), 4.16 (q, $J = 7.03$ Hz, 2H, OCH_2CH_3), 4.14 (s, 3H, OMe), 3.11 (s, 3H, NMe), 1.35 (t, $J = 7.16$ Hz, 3H, OCH_2CH_3), 1.31 (t, $J = 7.03$ Hz, Hz, 3H, OCH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 18.40$, 18.52, 33.95, 50.90, 51.35, 51.89, 88.18, 111.14, 116.61, 118.56, 121.70, 126.65, 128.09, 130.53, 136.09, 158.50, 165.01. Anal. calcd. (%) for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found (%): C, 61.00; H, 6.14; N, 4.07.

2-Methyl-3-(2-chlorophenyl)-4,5-dicarbomethoxy-Δ^4-isoxazoline (3i, $C_{14}H_{14}ClNO_5$). White crystals; mp 72.4–73.9 °C; IR (KBr): 1742, 1719, 1616, 1119 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.29–7.15$ (m, 4H, ArH), 5.09 (s, 1H, CH), 3.81 (s, 3H, Me), 3.62 (s, H, Me), 3.05 (s, 3H, Me). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 33.55$, 51.22, 52.30, 87.08, 112.99, 117.74, 119.25, 121.15, 126.75, 127.80, 128.30, 133.65, 164.18, 166.09. Anal. calcd. (%) for $C_{14}H_{14}ClNO_5$: C, 53.94; H, 4.53; N, 4.49. Found (%): C, 54.05; H, 4.35; N, 4.32.

2-Methyl-3-(2-chlorophenyl)-4,5-dicarboethoxy-Δ^4-isoxazoline (3j, $C_{16}H_{18}ClNO_5$). Colorless liquid; IR (KBr): 1742, 1719, 1628, 1121 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.19–7.00$ (m, 4H, ArH), 5.08 (s, 1H, CH), 4.20 (q, $J = 6.98$ Hz, Hz, 2H, OCH_2CH_3), 4.12 (q, $J = 7.13$ Hz, 2H, OCH_2CH_3), 3.09 (s, 3H, NMe), 1.33 (t, $J = 6.98$ Hz, 3H, OCH_2CH_3), 1.23 (t, $J = 7.13$ Hz, 3H, OCH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 19.14$, 20.32, 37.59, 58.48, 59.90, 95.17, 114.09, 117.78, 120.99, 122.32, 124.99, 126.94, 130.09, 136.00, 164.09, 165.14. Anal. calcd. (%) for $C_{16}H_{18}ClNO_5$: C, 56.56; H, 5.34; N, 4.12. Found (%): C, 56.58; H, 5.20; N, 3.99.

CONCLUSION

In conclusion, we have developed a simple and efficient synthesis of substituted Δ^4-isoxazolines via $TiCl_4$-catalyzed 1,3-dipolar cycloaddition under solvent-free conditions. Moreover, the relatively low cost of the catalyst, solvent-free condition, fast reaction times, simple experimental procedure, and excellent yields of the products are the advantages. We believe our procedure will find important applications in synthetic organic chemistry.

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