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A novel and direct synthesis of 1,3,4-oxadiazoles or oxazolines from carboxylic acids using cyanuric chloride/indium

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ABSTRACT

Direct synthesis of various oxazolines and 1,3,4-oxadiazoles from carboxylic acids was achieved using cyanuric chloride/indium under very mild conditions.

Five-membered heterocycles are privileged structures with utility in synthetic and medicinal chemistries.[1] In general, oxazoline and oxadiazole building blocks have found widespread applications as synthetic intermediates, protecting groups, pharmacophores, and ester and amide surrogates.[2–4] They also possess a wide spectrum of biological activities with antiinflammatory, antihypertensive, anticonvulsant, and analgesic properties.[5–7] Because of the importance of oxazolines and oxadiazoles, the development of simple and efficient protocols to prepare them using mild conditions has received much attention. Oxazolines and oxadiazoles are commonly prepared by a two-step method: coupling of carboxylic acids with amino alcohols and/or acylhydrazides followed by a dehydration step.[8–11] There are, however, few one-pot methods reported in the literature, with most being limited in substrate scope.[12] We recently reported an efficient, direct and common method for the synthesis of oxazolines and oxadiazoles from various carboxylic acids using the Deoxo-Fluor reagent.[13] The reaction was carried out in one-pot and was operationally simple and mild giving the products in high yields and purity in a very short time. For successful synthesis, it was necessary to use neat Deoxo-Fluor. When the reaction was carried out using Deoxo-Fluor in solution (such as THF and/or toluene), the efficiency, as well as yield, was reduced. Since neat Deoxo-Fluor is available only in North America and supplied only in solution (THF and toluene) in Europe and elsewhere, we wished to develop a convenient one-pot method for the synthesis of these useful heterocycles using reagents available to researchers worldwide. We therefore investigated the possibility of synthesizing oxazolines and oxadiazoles from carboxylic acids using an inexpensive and readily available reagent, such as 2,4,6-trichloro[1,3,5]triazine (cyanuric chloride, TCT). Cyanuric chloride has been reported as an efficient coupling reagent in the preparation of amides, esters, and anhydrides.[14] In this report, we describe a new, simple, and efficient synthesis of oxazolines and oxadiazoles directly from carboxylic acids using cyanuric chloride.

Recently, Bandgar and Pandit reported the use of 2-chloro-4,6-dimethoxy-1,3,5-triazine as a simple, mild, and highly efficient promoter for the synthesis of oxazolines.[8a] Their major product was, however, ω-hydroxyamides instead of oxazolines.[15] We employed this procedure, but used cyanuric chloride instead of 2-chloro-4,6-dimethoxy-1,3,5-triazine. Although the reaction times were long and yields were modest, we were delighted to observe that cyanuric chloride promoted coupling and cyclodehydration at the same time (Scheme 1).

The use of cyanuric chloride as coupling reagent typically involves the initial formation of an *N*-methylmorpholine: cyanuric chloride complex in CH_2Cl_2 or CH_3CN. Once this complex is formed, a carboxylic acid is added to generate the activated carboxylic acid, which upon further treatment with amine gives the corresponding amides.[16] After considerable experimentation with reaction of carboxylic acids with cyanuric chloride, we identified CH_2Cl_2 and pyridine as the optimal solvent and base, respectively.[17] In addition, to ensure an elegant and efficient synthesis of target heterocycles under very mild and shorter reaction times the addition of a catalytic amount of indium (In) metal is necessary.[18] Typically, the carboxylic acid (0.43 mmol, 1 equiv) and cyanuric chloride (0.65 mmol, 1.5 equiv) were dissolved in CH_2Cl_2 (5 ml) in an open test tube. Pyridine (1.3 mmol, 3 equiv) was added drop wise at 0 °C, and a white suspension was formed after occasional vortex mixing. After 15 min, 2-amino-2-methyl-1-propanol (1.2 mmol, 3 equiv) was added (portion wise), followed by addition of indium (0.065 mmol, 0.15 equiv) at room temperature. The reaction mixture was occasionally shaken on a vortex mixer until oxazoline formation was complete (monitored by TLC and GC–MS). Table 1 shows the results obtained from the direct reaction of various carboxylic acids with 2-amino-2-methyl-1-propanol. The products were generally recovered in pure form and in high yields simply by concentration of solvent extracts under reduced pressure. The

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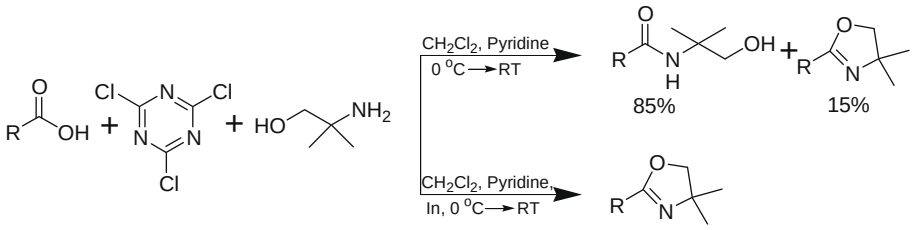

Scheme 1. Effect of Indium on oxazoline cyclization.

Table 1
Direct cyclization of carboxylic acids to oxazolines using cyanuric chloride/indium

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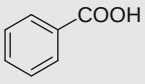
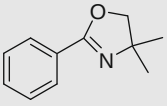
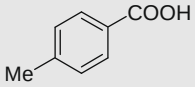
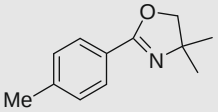
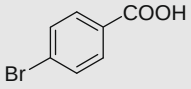
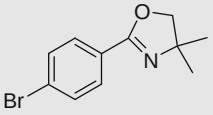
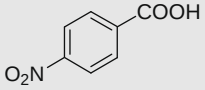
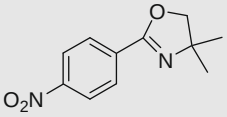
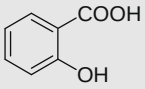
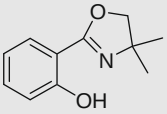
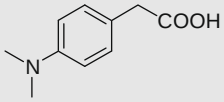
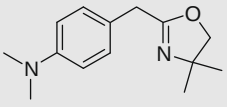
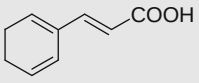
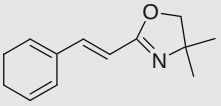
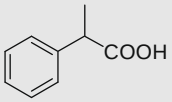
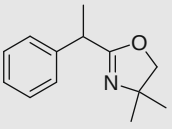
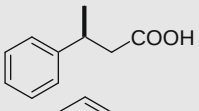
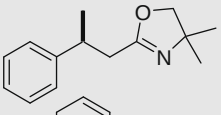
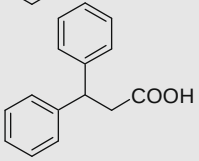
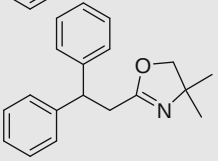
1			88	35
2			90	35
3			80	20
4			88	20
5			92	30
6			86	40
7			90	30
8			85	30
9			90	35
10			90	30

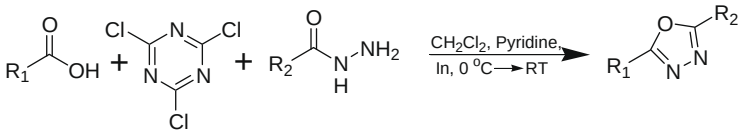
[a] Yields of pure, isolated products (characterized by GC–MS, and ^{1}H and ^{13}C NMR).

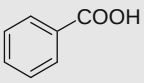
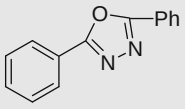
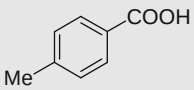
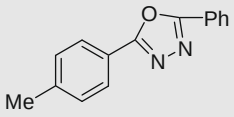
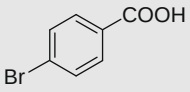
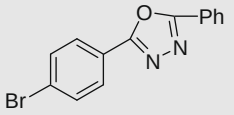
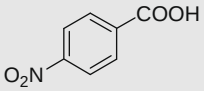
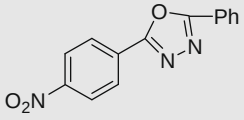
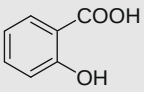
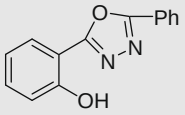
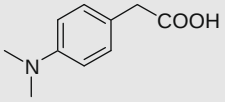
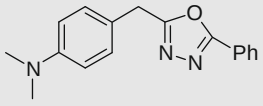
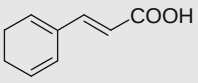
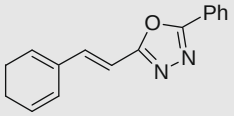
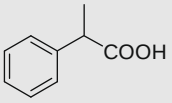
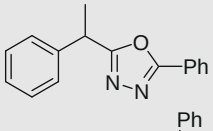
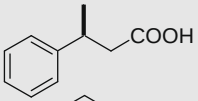
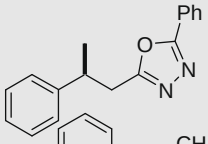
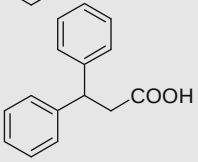
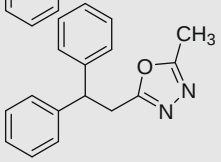
triazine byproducts were easily removed by simple aqueous work-up. Both aromatic (Table 1, entries 1–5) and aliphatic (entries 6–10) carboxylic acids converted efficiently to the corresponding oxazoles. All reactions resulted in high isolated yields, and conver-

sion of carboxylic acid was complete as determined by GC–MS. This method was also applicable to *ortho*-substituted carboxylic acids, such as salicylic acid to give 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-phenol (entry 4) along with $\leqslant$10% of the 2-(2-chlorophenyl)-4,4-dimethyl-4,5-dihydrooxazole.

These encouraging results motivated us to speculate that a one-pot process for the synthesis of oxadiazoles under very mild condition might be possible. Fortunately, following the above protocol, we were able to prepare 1,3,4-oxadiazoles very efficiently at room temperature, simply by increasing the amount of indium catalyst to 0.30 equiv. Moreover, the best results were obtained using 3 equiv of TCT and 2 equiv of pyridine. This one-pot method was found to be quite general and worked well for a variety of alkyl and aryl carboxylic acids, as well as alkyl and aryl acid hydrazides (Table 2). Both aromatic and aliphatic carboxylic acids were smoothly converted to 1,3,4-oxadiazoles. Benzoic acids with electron-withdrawing

Table 2
Direct cyclization of carboxylic acids to oxadiazoles using cyanuric chloride/indium



Entry	Substrate	Product	Yield[a] (%)	Time (h)
1			89	6
2			85	6
3			80	2
4			85	2
5			87	3
6			82	4
7			86	3
8			85	4
9			85	8
10			92	2

[a] Yields of pure, isolated products (characterized by GC–MS, and ^{1}H and ^{13}C NMR).

groups (entries 3 and 4) were significantly better candidates than their electron-rich or neutral carboxylic acids (entries 1 and 2).

To demonstrate the efficiency of this method, we also reacted cinnamic acid as well as salicylic acid (entries 5 and 6) with acid hydrazides to give the corresponding oxadiazoles, which were not easily accessible by previous methods, in high yields. As can be seen from the Table 2, aliphatic carboxylic acids were also converted in good yields to the corresponding oxadiazoles (entries 8 and 10). In addition, the optically active oxadiazoles were also prepared (entry 9) by this method, with no racemization being observed by chiral GC analysis.[19]

In conclusion, we have developed an inexpensive, efficient, straightforward, and common method for the synthesis of oxazolines and oxadiazoles from various carboxylic acids using cyanuric chloride. The reaction is carried out in one-pot and is operationally simple and gives products with high yields and purity. Moreover, this process is amenable to scale-up.

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References and notes

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19. In a typical procedure, the carboxylic acid (0.43 mmol, 1 equiv) and cyanuric chloride (1.3 mmol, 3 equiv) were dissolved in CH_2Cl_2 (5 ml) in an open test tube. Pyridine (0.86 mmol, 2 equiv) was added dropwise, a white suspension was formed on vortexing occasionally. After 15 min acid hydrazide (1.2 mmol, 3 equiv) was added (portionwise) followed by indium (0.13 mmol, 0.30 equiv) at room temperature. The reaction mixture was occasionally shaken on a vortex mixer at room temperature until formation of oxadiazoles was completed as determined by TLC and GC–MS analysis. (*S*)-2-Phenyl-5-(2-phenylpropyl)-[1,3,4]oxadiazole (Table 2, entry 9). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98(d, J = 7.4 Hz, 2H), 7.54–7.48 (m, 3H), 7.34–7.28 (m, 4H), 7.25(t, J = 7.4 Hz, 1H), 3.42(m, 1H), 3.22 (dd, J = 12.0 Hz, 2H), 1.43(d, J = 6.0 Hz, 3H); GC–FID: (Chiraldex$^{\text{TA}}$, 50 °C, 5 min, 2 °C/min to 160 °C, 10 min.), t_R: 16.81 min (99% ee). $[\alpha]_D$ +8.23 (*c* 0.10, EtOH); GC: (HP-5, 50 °C, 2 min, 20 °C/min to 260 °C, 5 min, 40 °C/min to 300 °C, 10 min), t_R: 11.95 min. MS (EI) *m/z* (relative intensity): 264 ($M^{+\cdot}$, 52), 249 (24), 160 (60), 105 (100).*2-(2,2-Diphenylethyl)-5-methyl-[1,3,4]oxadiazole* (Table 2, entry 10). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38–7.18 (m, 10H), 4.52 (m, 1H), 3.05 (d, J = 6.0 Hz, 2H), 2.45 (s, 3H); GC: (HP-5, 50 °C, 2 min, 20 °C/min to 260 °C, 5 min, 40 °C/min to 300 °C, 10 min), t_R: 11.85 min. MS (EI) *m/z* (relative intensity): 264 ($M^{+\cdot}$, 45), 180 (10), 167 (100), 152 (25).*2-(2,2-Diphenylethyl)-4,4-dimethyl-4,5-dihydrooxazole* (Table 1, entry 10). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30–7.18 (m, 10H), 4.51 (m, 1H), 3.93 (s, 2H), 3.04 (d, J = 6.0 Hz, 2H), 1.05 (s, 6H); GC: (HP-5, 50 °C, 2 min, 20 °C/min to 260 °C, 5 min, 40 °C/min to 300 °C, 10 min), t_R: 11.20 min. MS (EI) *m/z* (relative intensity): 279 ($M^{+\cdot}$, 8), 264 (35), 167 (100), 152 (25), 77 (10).