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Mild, Efficient Friedel−Crafts Acylations from Carboxylic Acids Using Cyanuric Chloride and $AlCl_3$

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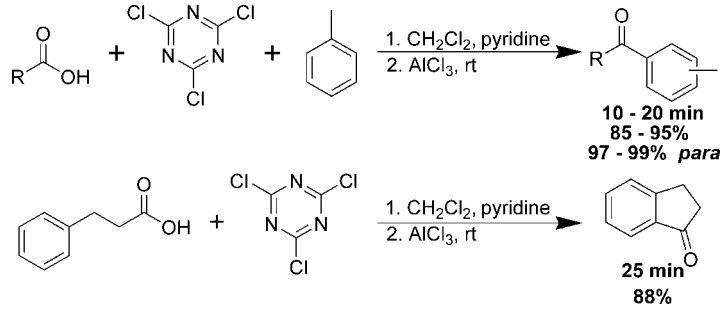
ABSTRACT



A mild method for Friedel−Crafts acylation with aromatic and aliphatic carboxylic acids using cyanuric chloride, pyridine, and $AlCl_3$ was developed. Both inter- and intramolecular acylations were achieved at room temperature in high yield and in very short reaction times.

Inter- and intramolecular Friedel−Crafts acylations are common and powerful methods for C−C bond formation and remain the subject of continued investigation. The Friedel−Crafts reaction has been widely used in the synthesis of aromatic and cyclic ketones, important synthetic intermediates in the chemical and pharmaceutical industries.[1] Typically, acid chlorides are used as the acylating agents with stoichiometric amounts of Lewis acids and high temperatures. This procedure suffers from inducing severe corrosion to the mechanical systems used in the process as well as waste problems, mainly because HCl is formed as a byproduct.

To minimize these problems, several new methods involving carboxylic acids, acid anhydrides, esters, and Meldrum's acids as the acylating agents have been used.[2−4] Carboxylic acids seem to be the best choice of acylating agents since they are common precursors of acid chlorides and anhydrides, and their reactions produce water, instead of HCl, as a byproduct.[5]

We wished to develop a Friedel−Crafts reaction that proceeds under very mild and simple conditions. Our choice of carboxylic acids as the acylating agents encouraged us to search for a reagent that could activate the acids for the coupling and at the same time increase the efficiency of the Lewis acid (e.g., $AlCl_3$) used. One such reagent was cyanuric chloride (2,4,6-trichloro-1,3,5-triazine; TCT), which is readily commercially available and inexpensive, making it a logical

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(1) (a) Heaney, H. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 2, pp 733−752. (b) Olah, G. A. *Friedel-Crafts Chemistry*; Wiley: New York, 1973. (c) Roberts, R. M.; Khalaf, A. A. *Friedel-Crafts Alkylation Chemistry, A Century of Discovery*; Marcel Dekker: New York, 1984. (d) Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. *Comprehensive Organic Synthesis*, 1st ed.; Pergamon: New York, 1991; Vol. 3, pp 293−339. (e) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550–556. (f) Bandini, M.; Emer, E.; Tommasi, S.; Umani-Ronchi, A. *Eur. J. Org. Chem.* **2006**, 3527−3544. For reviews on the intramolecular Friedel−Crafts acylation reaction, see: (g) Heaney, H. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 2, pp 753−768. (h) Sethna, S. *Friedel-Crafts and Related Reactions*; Olah, G. A., Ed.; Interscience: New York, 1964; Vol. 3, pp 911−1002. (i) Gore, P. H. *Chem. Rev.* **1955**, *55*, 229–281.

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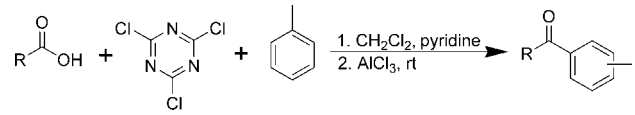
choice.[6] Here we report a very simple and highly efficient method for the synthesis of aromatic and cyclic ketones using carboxylic acids in the presence of cyanuric chloride and $AlCl_3$ under mild conditions.

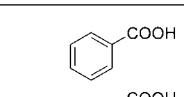
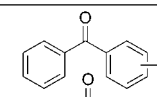
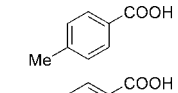
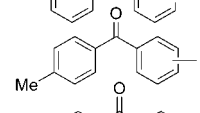
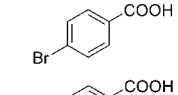
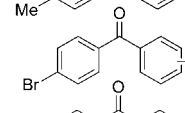
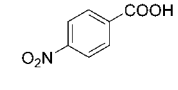
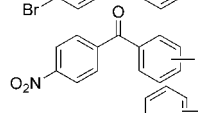
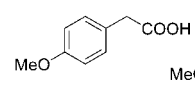
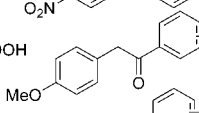
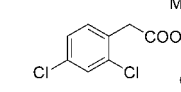
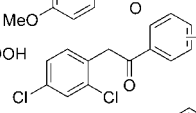
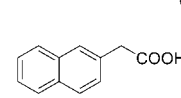
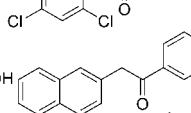
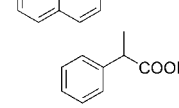
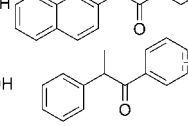
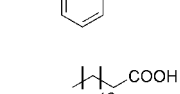
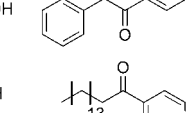
Cyanuric chloride is useful for the synthesis of alcohols, diazocarbonyl, acyl azides, and hydroxamic acids as well as acyl chlorides from carboxylic acids.[7,8] Use of a 1:1:1 molar ratio of carboxylic acid−cyanuric chloride−amine is known to provide the acid chloride at room temperature.[8b] We hypothesized that an acyl chloride formed in such a way could be used in the same pot for direct synthesis of ketones via the Friedel−Crafts reaction, and at the same time the HCl byproduct from $AlCl_3$ could be buffered by an amine base. We found this to be true, plus we were pleasantly surprised to find that the acylation occurred rapidly and at room temperature.

Mixing cyanuric chloride with carboxylic acids gave no reaction with toluene under a variety of attempted conditions. However, mild and expedient formation of the activated form of the acid in less than 15 min was achieved by adding pyridine dropwise to the mixture of cyanuric chloride and carboxylic acid in CH_2Cl_2 at room temperature. Typically, the carboxylic acid (0.43 mmol, 1 mol equiv) and cyanuric chloride (0.69 mmol, 1.6 mol equiv) were dissolved in CH_2Cl_2 (5 mL) in an open test tube, and then pyridine (0.43 mmol, 1 mol equiv) was added dropwise at room temperature. The suspension that formed was occasionally agitated on a vortex mixer. After 15 min at room temperature, $AlCl_3$ (0.52 mmol, 1.2 mol equiv) was added portion-wise, followed by addition of excess toluene. The reaction mixture was occasionally shaken on a vortex mixer at room temperature for 5−20 min until conversion to the ketone was complete (monitored by TLC and GC-MS analyses).

Interestingly, in all cases, very high regioselective carbonylation took place at the *para* position. Encouraged by the remarkable activity of the cyanuric chloride/pyridine/$AlCl_3$ system as a means to achieve acylation, we examined the scope and limitations of its use in intermolecular Friedel−Crafts reactions of toluene with various aliphatic as well as aromatic carboxylic acids (Table 1). Aliphatic carboxylic acids and aromatic carboxylic acids bearing either electron-donating

Table 1. Intermolecular Friedel−Crafts Acylations of Carboxylic Acids with Toluene in the Presence of Cyanuric Chloride/$AlCl_3$ at Room Temperature



entry	substrate	product	reaction time yield (%)[a] *para:ortho*	literature reaction condition with acid chloride, time, yield (%) *para:ortho*
1			20 min (95) 99:1	rt, 4 h, (80) 1.1 equiv of $AlCl_3$ ≥80:20, (ref. 10a)
2			10 min (90) 99:1	rt, 4 h, (68) 1.1 equiv of $AlCl_3$ ≥70:30, (ref. 10a)
3			15 min (90) 98:2	reflux, 3 h, (89) 1.5 equiv of $AlCl_3$ ≥90:10, (ref. 10b)
4			20 min (85) 97:3	rt, 90 min, (80) 1.3 equiv of $AlCl_3$ ≥80:20, (ref. 10c)
5			10 min (95) 99:1	—
6			10 min (92) 98:2	—
7			10 min (95) 99:1	—
8			10 min (85) 98:2	—
9			10 min (90) 99:1	—

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

(2) For recent examples, see: (a) Kawada, A.; Mitamura, S.; Matsuo, J.; Tsuchiya, T.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2325−2333. (b) Singh, R. P.; Kamble, R. M.; Chandra, K. L.; Saravanan, P.; Singh, V. K. *Tetrahedron* **2001**, *57*, 241–247. (c) Duris, F.; Barbier-Baudry, D.; Dormond, A.; Desmurs, J. R.; Bernard, J. M. *J. Mol. Catal. A: Chem.* **2002**, *188*, 97–104. (d) Le Roux, C.; Dubac, J. *Synlett* **2002**, 181–200. (e) Prakash, G. K. S.; Yan, B.; Torok, B.; Bucsi, I.; Tanaka, M.; Olah, G. A. *Catal. Lett.* **2003**, *85*, 1–6. (f) Sheemol, V. N.; Tyagi, B.; Jasra, R. V. *J. Mol. Catal. A: Chem.* **2004**, *215*, 201–208. (g) Hardacre, C.; Katdare, S. P.; Milroy, D.; Nancarrow, P.; Rooney, D. W.; Thompson, J. M. *J. Catal.* **2004**, *227*, 44–52. (h) Nakamura, H.; Arata, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1893–1896. (i) Matsushita, Y.; Sugamoto, K.; Matsui, T. *Tetrahedron Lett.* **2004**, *45*, 4723–4727. (j) Earle, M. J.; Hakala, U.; Hardacre, C.; Karkkainen, J.; McAuley, B. J.; Rooney, D. W.; Seddon, K. R.; Thompson, J. M.; Wähälä, K. *Chem. Commun.* **2005**, 903–905. (k) Hao, X.; Yoshida, A.; Nishikido, *Tetrahedron Lett.* **2005**, *46*, 2697–2700. (l) Arai, S.; Sudo, Y.; Nishida, A. *Tetrahedron* **2005**, *61*, 4639–4642. (m) Xiao, Y.; Malhotra, S. V. *J. Organomet. Chem.* **2005**, *690*, 3609–3613. (n) Zane, F.; Melada, S.; Signoretto, M.; Pinna, F. *Appl. Catal., A* **2006**, *299*, 137–144.

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(5) (a) Sartori, G.; Maggi, R. *Chem. Rev.* **2006**, *106*, 1077–1104. (b) Chiche, B.; Finiels, C.; Gauthier, A.; Geneste, P. *J. Org. Chem.* **1986**, *51*, 2128–2130. (c) Gauthier, C.; Chiche, B.; Finiels, A.; Geneste, P. *J. Mol. Catal.* **1989**, *50*, 219–229. (d) Wang, Q. L.; Ma, Y.; Ji, X.; Yan, H.; Qiu, Q. *J. Chem. Soc., Chem. Commun.* **1995**, 2307–2308. (e) Singh, A. P.; Pandey, A. K. *J. Mol. Catal. A: Chem.* **1997**, *123*, 141–147. (f) Pandey, A. K.; Singh, A. P. *Catal. Lett.* **1997**, *44*, 129–133. (g) De Castro, C.; Primo, J.; Corma, A. *J. Mol. Catal. A: Chem.* **1998**, *134*, 215–222. (h) Izumi, Y.; Ogawa, M.; Nohara, W.; Urabe, K. *Chem. Lett.* **1992**, 1987–1990. (i) Kaur, J.; Kozhevnikov, I. V. *Chem. Commun.* **2002**, 2508–2509. (j) Firouzabadi, H.; Iranpoor, N.; Nowrouzi, F. *Tetrahedron* **2004**, *60*, 10843–10850. (k) Chiche, B.; Finiels, A.; Gautheir, C.; Geneste, P. *J. Mol. Catal.* **1987**, *42*, 229–235. (l) Suzuki, K.; Kitagawa, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3729–3734. (m) Kobayashi, S.; Moriwaki, M.; Hachiya, I. *Tetrahedron Lett.* **1996**, *37*, 4183–4186. (n) Walker, M. U. S. Patent 5,362,375, 2002, *Chem. Abstr.*, **2002**, *136*, 262−987. (o) Earle, M. J.; Hakala, U.; McAuley, B. J.; Nieuwenhuyzen, M.; Ramani, A.; Seddon, K. R. *Chem. Commun.* **2004**, 1368–1369. (p) Sarvari, M. H.; Sharghi, H. *Helv. Chim. Acta* **2005**, *88*, 2282–2287.

(6) (a) Blotny, G. *Tetrahedron* **2006**, *62*, 9507–9522. (b) Haval, K. P. *Synlett* **2006**, 2156–2157.

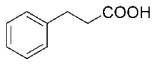
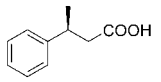
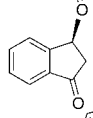
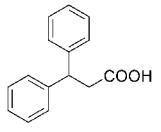
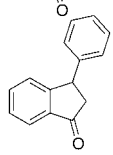
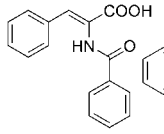
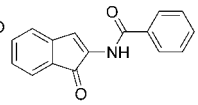
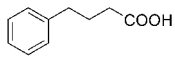
(7) (a) Falorni, M.; Porcheddu, A.; Tadei, M. *Tetrahedron Lett.* **1999**, *40*, 4395–4396. (b) Forbes, D. C.; Barrett, E. J.; Lewis, D. L.; Smith, M. C. *Tetrahedron Lett.* **2000**, *41*, 9943–9947. (c) Bandgar, B. P.; Pandit, S. S. *Tetrahedron Lett.* **2002**, *43*, 3413–3414. (d) Giacomelli, G.; Porcheddu, A.; Salaris, M. *Org. Lett.* **2003**, *5*, 2715–2717.

(8) (a) Luo, G.; Xu, L.; Poindexter, G. S. *Tetrahedron Lett.* **2002**, *43*, 8909–8912. (b) Venkataraman, K.; Wagle, D. R. *Tetrahedron Lett.* **1979**, *20*, 3037–3040.

or electron-withdrawing groups were converted into the corresponding ketones in very short reaction times and in good to excellent yields at room temperature. Use of benzene instead of toluene under the same reaction conditions afforded the respective ketone with excellent yield (data not shown).

The efficiency and the ease of the reaction setup led us to investigate intramolecular Friedel−Crafts reactions. It is well-known that it is more difficult to form five-membered rings by Friedel−Crafts cyclization than it is to make six-membered rings.[9] Yet, our procedure was equally successful in the preparation of 1-tetralone and various 1-indanones. As shown in Table 2, all the substrates participated very efficiently in the reaction to afford the cyclized product in very short times and excellent yields. The efficacy of this method was explored with 2-benzylamino-3-phenylacrylic acid (Table 2, entry 4) which was converted to *N*-(1-oxo-1*H*-inden-2-yl)benzamide as the only product in less than 25 min at room temperature. This is the first report of Friedel−Crafts cyclization being performed with carboxylic acids at room temperature in such a short time. Moreover, this method can also be successfully applied on a large scale (see Supporting Information).

Table 2. Intramolecular Friedel−Crafts Acylations of Carboxylic Acids in the Presence of Cyanuric Chloride/$AlCl_3$ at Room Temperature

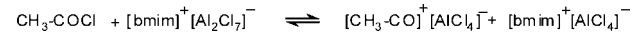
entry	substrate	product	reaction time yield (%)	literature reaction condition with acid chloride, time, yield (%)
1			25 min (88)	reflux, 3 h (67) (ref. 10d)
2			25 min (90)	——
3			25 min (95)	reflux, 3 h (75) (ref. 10e)
4			25 min (85)	reflux, 3 h (67) (ref. 10f)
5			25 min (95)	rt, 3 h (72) (ref. 10g)

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

Since there are no reports of direct Friedel−Crafts acylations from carboxylic acids in the presence of $AlCl_3$, we show comparisons between the reported methods, where acyl chlorides were used as the acylating agent, and our method in Tables 1 and 2.[10]

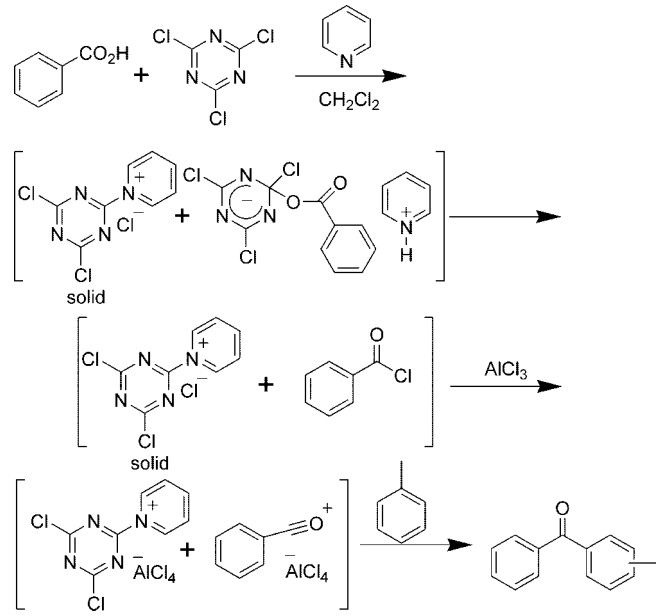
The mechanism through which these conversions might occur is debatable. The literature shows that the acidic ionic liquid formed by mixing $AlCl_3$ and 1-butyl-3-methylimidazolium chloride in a 1:1 or 2:1 ratio gives the Lewis acidic species $Al_2Cl_7^-$.[11] Moreover, a stoichiometric reaction between acetyl chloride and $Al_2Cl_7^-$ occurs in this ionic liquid (Scheme 1).

Scheme 1



Our conditions could cause conversion of $AlCl_3$ to the more reactive $Al_2Cl_7^-$, which has much higher Lewis acidity. On the basis of the similarity between cyanuric chloride-pyridine adducts/$AlCl_3$ and acidic ionic liquid/$AlCl_3$, a plausible mechanism might be as follows (Scheme 2).

Scheme 2



There are certainly alternative mechanisms. One might be that the interaction of cyanuric chloride with carboxylic acid

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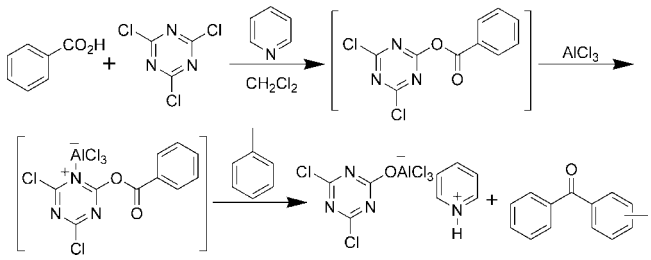
in the presence of pyridine in CH_2Cl_2 leads to formation of an activated ester, which subsequently might react with $AlCl_3$ to furnish a Lewis complex. The treatment of this complex with toluene might then lead to the ketone (Scheme 3).

Scheme 3



We should mention that the traditional Friedel−Crafts reaction using benzoyl chloride and $AlCl_3$ in CH_2Cl_2 causes vigorous release of, and increased reaction vessel pressure by, HCl gas, a phenomenon not observed in our method. It is likely that the pyridine used in our conditions captures the HCl, making the reaction far safer.

In summary, we have found an efficient and new one-pot, two-step method for the synthesis of various aliphatic and aromatic ketones from carboxylic acids using the Friedel−Crafts reaction. The method was also extended to intramolecular Friedel−Crafts reactions to provide 1-tetralone and 1-indanones in excellent yields. The notable advantages of this procedure are its (a) operational simplicity, (b) remarkable efficiency toward inter- and intramolecular Friedel−Crafts reactions, (c) general applicability to aromatic and aliphatic carboxylic acids, (d) reaction conditions that are tolerant of a variety of sensitive functional groups, and (e) high yields. This protocol provides a practical alternative to the existing methods available for the synthesis of ketones and cyclic ketones from their corresponding carboxylic acids.

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Supporting Information Available: Descriptions of the general methods and spectroscopic data (^1H and ^{13}C NMR) for all products are given in the supplementary data. This material is available free of charge via the Internet at http://pubs.acs.org.

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