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Convenient Access to Polysubstituted 1-Indanones by $Sc(OTf)_3$-Catalyzed Intramolecular Friedel–Crafts Acylation of Benzyl Meldrum's Acid Derivatives

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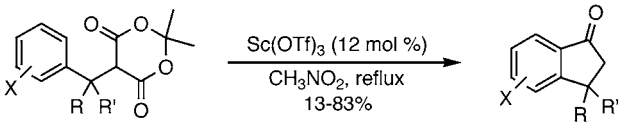
ABSTRACT



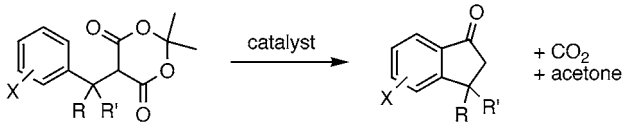
The intramolecular Friedel–Crafts acylation of benzyl Meldrum's acids is catalyzed by $Sc(OTf)_3$ under mild reaction conditions. Several polysubstituted 1-indanones have been prepared.

The intramolecular Friedel−Crafts reaction is a general and convenient method for the synthesis of 1-indanones, 1-tetralones, and related aromatic ketones.[1] Such carbocycles have proven synthetic utility in numerous pharmaceuticals and biologically active natural products.[2] The importance of this transformation has generated great interest in the development of a catalytic Friedel−Crafts acylation under mild reaction conditions.

Despite considerable progress made in the development of Lewis acid catalyzed protocols,[3] the cyclization precursors are essentially limited to carboxylic acids and acid chlorides.[4] Progress toward a truly mild and operationally simple Friedel−Crafts reaction would be aided by the availability of a moisture-stable, highly electrophilic precursor that is easily prepared, functionalized, and purified, preferably by recrystallization. Friedel−Crafts acylation of such a precursor should provide aromatic ketones catalytically at moderate temperatures and be sufficiently flexible to assemble polycyclic ring systems rapidly and modify substitution within the rings.

Meldum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) is a versatile reagent that can be easily functionalized at the 5-position.[5] It is highly susceptible to nucleophilic attack at the carbonyl carbons. As illustrated in Scheme 1, the arylation of Meldrum's acid derivatives would lead to inert side products: CO_2 and acetone.[6] Exploiting the high electrophilicity, stability, easy access, and purification of Meldrum's acid derivatives, we herein report an intramolecular Friedel−

Scheme 1. Meldrum's Acid Derivatives in the Lewis Acid Catalyzed Intramolecular Friedel−Crafts Acylation



(1) (a) Olah, G. *Friedel−Crafts Chemistry*; Wiley-Interscience: New York, 1973. (b) Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 733−752 and 753−768.

(2) (a) Gagnier, S. V.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 4804−4807. (b) Adams, D. R.; Duncton, M. A. J. *Synth. Commun.* **2001**, *31*, 2029−2036. (c) Bös, M.; Jenck, F.; Martin, J. R.; Moreau, J.-L.; Sleight, A. J.; Wichmann, J.; Widmer, U. *J. Med. Chem.* **1997**, *40*, 2762−2769. (d) Sugimoto, H.; Iimura, Y.; Yamanishi, Y.; Yamatsu, K. *J. Med. Chem.* **1995**, *38*, 4821−4829.

(3) For rare earth triflate catalysts in the intramolecular Friedel−Crafts reaction of aromatics with carboxylic acids, see: (a) Cui, D.-M.; Kawamura, M.; Shimada, S.; Hayashi, T.; Tanaka, M. *Tetrahedron Lett.* **2003**, *44*, 4007−4010. For an example of protic acid-catalyzed Friedel−Crafts acylation, see: (b) Yamato, T.; Hideshima, C.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1991**, *56*, 3955−3957.

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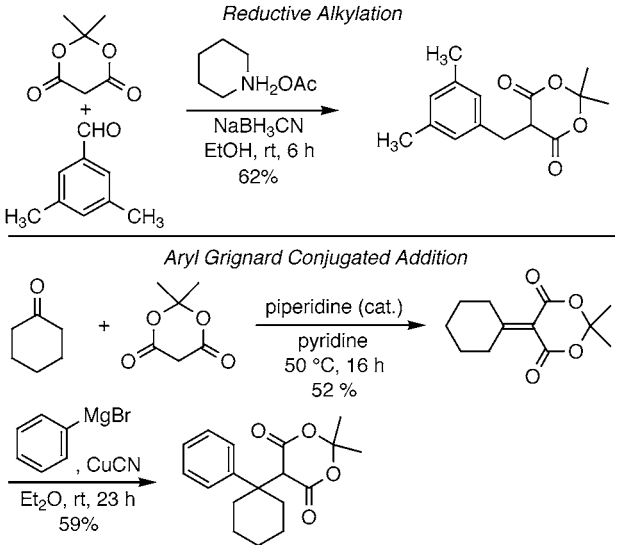
Crafts acylation protocol of benzyl Meldrum's acid derivatives catalyzed by $Sc(OTf)_3$ under mild reaction conditions. This method has been applied to the synthesis of polysubstituted 1-indanones.

Simple and versatile routes gave access to the Friedel–Crafts acylation precursors in one or two steps from Meldrum's acid (Scheme 2). A method was developed to

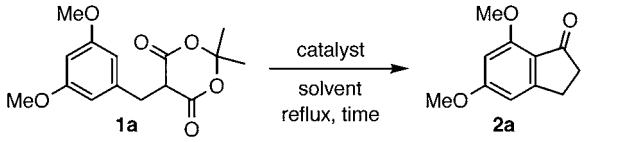
Scheme 2. Meldrum's Acid Derivatives Synthesis



prepare the methylene tethered Meldrum's acid derivatives by reductive alkylation. Substituted benzaldehydes were condensed with Meldrum's acid and the resulting alkylidene were reduced in situ with $NaBH_3CN$.[7] Mono- and disubstituted Meldrum's acid derivatives at the benzylic position were accessed via 1,4-conjugate addition of aryl Grignards to Meldrum's alkylidenes,[8] prepared by Knoevenagel condensation of Meldrum's acid with ketones.[9] The overall yields for the acylation precursor syntheses, which were prepared on multigram scale due to the availability of the starting materials, varied from good to modest. In most cases, the Meldrum's acid derivatives were purified by recrystallization.

The intramolecular acylation of arenes with Meldrum's acid derivatives was initiated with the electron-rich 3,5-dimethoxybenzene substrate **1a** searching for effective catalyst and reaction conditions. The Friedel–Crafts acylation of **1a** proceeded in refluxing CH_3NO_2 in the absence of catalyst and provided indanone **2a** in 52% yield (Table 1,

Table 1. Effect of Catalysts on the Acylation Reaction of **1a**



entry	catalyst	solvent	reaction time (h)	yield (%)
1		CH_3NO_2	3	52
2	TfOH (20 mol %)	$ClCH_2CH_2Cl$	2.75	38
3	TFA (20 mol %)	$ClCH_2CH_2Cl$	17	37
4	TMSOTf (20 mol %)	$ClCH_2CH_2Cl$	3	60
5	$Dy(OTf)_3$ (12 mol %)	CH_3NO_2	1	56
6	$Yb(OTf)_3$ (12 mol %)	CH_3NO_2	1	67
7	$Sc(OTf)_3$ (10 mol %)	$ClCH_2CH_2Cl$	4.5	72
8	$Sc(OTf)_3$ (8 mol %)	CH_3CN	2	68
9	$Sc(OTf)_3$ (12 mol %)	CH_3NO_2	1	73

entry 1). Attempts at improving the yield using protic acids in refluxing polar solvents failed (Table 1, entries 2–3), and 3-(3,5-dimethoxyphenyl)propanoic acid was formed as the major product. Indanone **2a** was isolated in good yield when **1a** was treated with TMSOTf (entry 4).

We next examined rare earth triflates, which have been reported to efficiently catalyze the intermolecular Friedel–Crafts acylation reaction of activated aromatics with anhydrides.[10] $Dy(OTf)_3$ was inefficient at improving the yield, but $Yb(OTf)_3$ enhanced the formation of **2a**, while decreasing reaction time (Table 1, entries 5 and 6). Indanone **2a** was obtained in 68–73% yield using 8–12 mol % of $Sc(OTf)_3$ in CH_3NO_2, CH_3CN, or $ClCH_2CH_2Cl$. In comparison with the thermal and TMSOTf-catalyzed acylations, the crude reaction mixture was cleaner and the product easy to isolate and purify.[11]

Using $Sc(OTf)_3$ in refluxing CH_3NO_2 or CH_3CN as the standard reaction conditions, the influence of substitution at the benzylic position on the acylation efficiency was examined (Table 2). Increased substitution improved the efficiency of the acylation reaction, and good yields (77–83%) of 3-substituted **2b** (entry 1) and 3,3-disubstituted-1-indanones **2c** and **2d** were obtained (entries 2 and 3). This effect was

(4) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999; pp 1422–1433.

(5) (a) Chen, B.-C. *Heterocycles* **1991**, *32*, 529–597. (b) McNab, H. *Chem. Soc. Rev.* **1978**, *7*, 345–358.

(6) The pyrolysis of 2,2-dimethyl-5-phenoxy-1,3-dioxane-4,6–dione at 450 °C provides a small amount of benzofuran-2(3*H*)-one via a proposed phenoxyketene intermediate; see: Crow, W. D.; McNab, H. *Aust. J. Chem.* **1979**, *32*, 111–121.

(7) For other reductive alkylation procedures, see: (a) Huang, X.; Xie, L. *Synth. Commun.* **1986**, *16*, 1701–1707. (b) Hrubowchak, D. M.; Smith, F. X. *Tetrahedron Lett.* **1983**, *24*, 4951–4954.

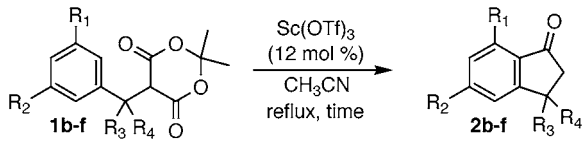
(8) (a) Vogt, P. F.; Molino, B. F.; Robichaud, A. J. *Synth. Commun.* **2001**, *31*, 679–684. (b) Davies, A. P.; Egan, T. J.; Orchard, M. G.; Cunningham, D.; McArdle, P. *Tetrahedron* **1992**, *48*, 8725–8738. (c) Larchevêque, M.; Tamagnan, G.; Petit, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 31–33. (d) Huang, X.; Chan, C.-C.; Wu, Q.-L. *Synth. React. Inorg. Met.-Org. Chem.* **1982**, *12*, 549–556. (e) Huang, X.; Chan, C.-C.; Wu, Q.-L. *Tetrahedron Lett.* **1982**, *23*, 75–76. (f) Haslego, M. L.; Smith, F. X. *Synth. Commun.* **1980**, *10*, 421–427.

(9) Baty, J. D.; Jones, G.; Moore, C. *J. Org. Chem.* **1969**, *34*, 3295–3302.

(10) (a) Kawada, A.; Mitamura, S.; Matsuo, J.-i.; Tsuchiya, T.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2325–2333. (b) For a recent review, see: Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227–2302.

(11) To determine if the byproduct acetone was causing side reactions that were decreasing the yield of the Friedel–Crafts acylation, a control reaction was performed by refluxing an equimolar amount of 1-indanone and acetone in the presence of a catalytic amount of $Sc(OTf)_3$ for 1 h. GC–MS and ^1H NMR analysis of the crude reaction mixture showed no decomposition of 1-indanone or formation of aldol products.

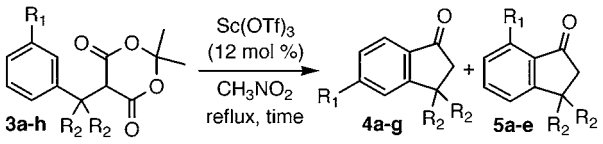
Table 2. Acylation of 3,5-Disubstituted Arenes



entry	substrate	reaction time (h)	product	yield (%)
1	**1b,** $R_1 = R_2 = OMe$; $R_3 = Me$; $R_4 = H$	2	**2b**	77
2	**1c,** $R_1 = R_2 = OMe$; $R_3 = R_4 = Me$	2	**2c**	82
3	**1d,** $R_1 = R_2 = OMe$; $R_3 = R_4 = -(CH_2)_5-$	2	**2d**	83
4	**1e,** $R_1 = R_2 = Me$; $R_3 = R_4 = H$	9	**2e**	52[a]
5	**1f,** $R_1 = R_2 = Me$; $R_3 = R_4 = -(CH_2)_5-$	1.5	**2f**	75[a]

[a] The reaction was run in CH_3NO_2.

Table 3. Acylation of 3-Mono- and Unsubstituted Arenes



entry	substrate	reaction time (h)	products (ratio)[a]	yield (%)
1	**3a**, $R_1 = OMe$; $R_2 = H$	1	**4a**/**5a** (5.5:1)	52
2	**3b**, $R_1 = OMe$; $R_2 = -(CH_2)_5-$	2	**4b**/**5b** (3.4:1)	71
3	**3c**, $R_1 = Me$; $R_2 = H$	1	**4c**/**5c** (1:1)	48
4	**3d**, $R_1 = Me$; $R_2 = -(CH_2)_5-$	2	**4d**/**5d** (1:1)	62
5	**3e**, $R_1 = Cl$; $R_2 = H$	2		trace
6	**3f**, $R_1 = Cl$; $R_2 = -(CH_2)_5-$	2	**4e**/**5e** (2:1)	62
7	**3g**, $R_1 = R_2 = H$	9	**4f**	13[b]
8	**3h**, $R_1 = H$; $R_2 = -(CH_2)_5-$	0.5	**4g**	56[c]

[a] Determined by analysis of the crude ^1H NMR. [b] Substrate **3g** was added over 9 h to a refluxing solution of $Sc(OTf)_3$ by syringe pump, followed by an additional 2 h of reflux. The one-pot procedure failed to produce indanone **4f**. [c] A yield of 57% was obtained when the slow addition procedure was used.

more pronounced for the 3,5-dimethylbenzene substrates than for the dimethoxy compounds (entries 4 and 5), but comparable yields were observed when the benzylic position was disubstituted (entries 3 and 5). Slow addition of the substrate to a solution of the Lewis acid did not improve the acylation yield for substrate **1f** (9-h slow addition gave **2f** in 73%). However, when indanone **2e** was prepared using the slow addition procedure, the yield was enhanced from 36% to 52%.

Having established the reactivity of Meldrum's acid derivatives with π-nucleophiles in the presence of $Sc(OTf)_3$, this acylation protocol was applied to mono- and unsubstituted aromatics. The importance of substitution at the benzylic position was prominent for substrates bearing a weak π-nucleophilic moiety[12] (Table 3). Regioisomeric indanones **4a** and **5a** were obtained from the monomethoxy substrates **3a** in modest yield (Table 3, entry 1). In comparison, disubstituted substrate **3b** gave a respectable yield of indanones **4b** and **5b**.

Substrate **3g** gave a low 13% yield of 1-indanone **4f** using the slow addition protocol, but the disubstituted substrate **3h** yielded 56% of **4g** under the standard conditions. Friedel–Crafts acylation of **3h** in the absence of $Sc(OTf)_3$ provided no trace of indanone after 24 h in refluxing CH_3NO_2, returning starting material.

A similar trend was observed for the cyclization of **3c** and **3d**. Deactivated *m*-chloro substrate **3f** provided a mixture of indanones **4e** and **5e** in 62% yield. Without any benzylic substituent, only trace formation of 1-indanone was detected using the slow addition method with substrate **3e**.

Three plausible reaction pathways for the intramolecular reaction of benzyl Meldrum's acid derivatives are illustrated in Scheme 3. Initial activation of the Meldrum's acid carbonyl group by $Sc(OTf)_3$ is key in all three pathways.

In Scheme 3 (*reaction pathway a*), $Sc(OTf)_3$ promotes tautomerization of benzyl Meldum's acid derivative to the corresponding 6-hydroxydioxinone. Enolized Meldrum's acids have been reported to cyclorevert leading to highly electrophilic acylketene intermediates.[13,14] Arylation of the Lewis acid activated acylketene yields an 1-indanone-2-carboxylic acid that further decarboxylates.[15]

The Lewis acid activated Meldrum's acid could directly participate in the acylation process as depicted in Scheme 3 (reaction pathway b). Following acylation, subsequent loss of acetone and CO_2 provides the indanone. This pathway parallels the conventional Friedel–Crafts acylation of arenes with anhydrides and acid chlorides.[1]

Finally, Meldrum's acid ring-opening reaction accompanied by the loss of acetone and CO_2 generates a ketene (Scheme 3, reaction pathway c) that further participates in the acylation process.[16]

Investigation of reaction pathway a proceeded by methylation of **1a** with Meerwein's salt to produce an α-oxoketene

(12) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66–77.

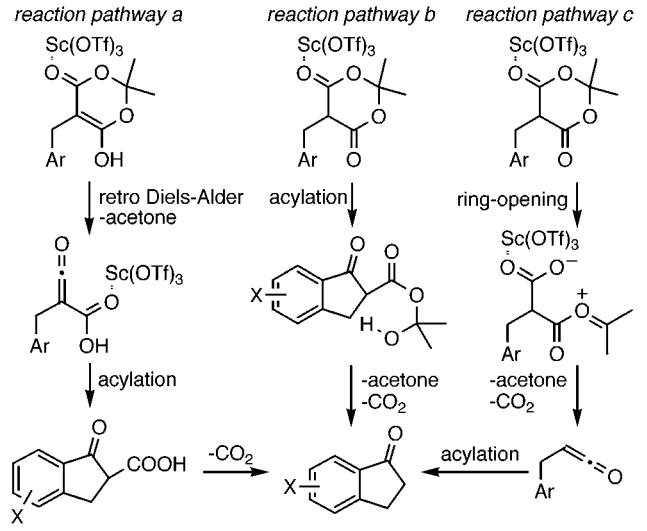
(13) (a) Sato, M.; Bann, H.; Kaneko, C. *Tetrahedron Lett.* **1997**, *38*, 6689–6692. (b) Bihlmayer, G. A.; Schuster, P.; Polansky, O. E. *Monatsh. Chem.* **1966**, *97*, 145–149.

(14) For a review on α-oxoketenes, see: Wentrup, C.; Heilmayer, W.; Kollenz, G. *Synthesis* **1994**, 1219–1248.

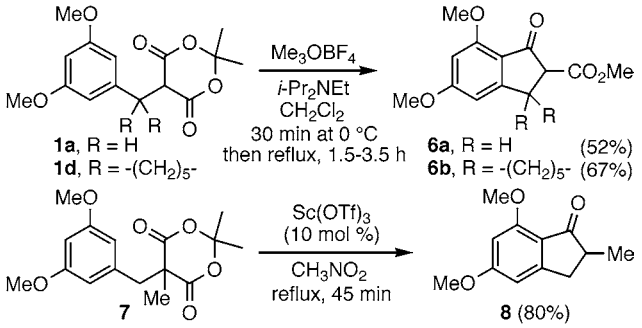
(15) (a) For an example of Friedel–Crafts acylation of chromium–carbene-complex-derived ketenes catalyzed by $ZnCl_2$, see: Bueno, A. B.; Moser, W. H.; Hegedus, L. S. *J. Org. Chem.* **1998**, *63*, 1462–1466. For intermolecular Friedel–Crafts arylation of ketenes, see: (b) Williams, J. W.; Osborn, J. M. *J. Am. Chem. Soc.* **1939**, *61*, 3438–3439. (c) Hurd, C. *J. Am. Chem. Soc.* **1925**, *47*, 2777–2780.

(16) Gaber, A. E.-A. O.; McNab, H. *Synthesis* **2001**, 2059–2074.

Scheme 3. Proposed Reaction Pathways



Scheme 4. Studies on the Acylation Mechanism



intermediate via cycloreversion of the resulting 6-methoxydioxinone. Intramolecular arylation of the acylketene intermediate was anticipated to produce a β-ketoester incapable of decarboxylation. Gratifyingly, 1-indanone-2-methyl ester **6a** was formed in 52% yield demonstrating the reactivity of acylketenes in acylation reactions (Scheme 4). Similarly, disubstituted substrate **1d** gave indanone **6b**.

In an attempt to suppress reaction pathway a, the nonenolizable substrate **7** was subjected to the optimized reaction conditions (Scheme 4). Efficient formation of 2-methyl-1-indanone **8** in 80% yield was realized,[17] supporting reaction pathways b and c in Scheme 3. Enolization of Meldrum's acid derivatives is therefore not a prerequisite for the acylation to proceed.

At this point, the reaction mechanisms have not been differentiated, and the overall acylation process may simultaneously proceed via any of the three pathways. The important yield enhancement when the Meldrum's acid substrate is substituted at the benzylic position may be an indication that the acylation occurs via a ketene intermediate. α-Substitution has been demonstrated to significantly increase the stability of α-oxoketenes.[13a]

In conclusion, we have disclosed a mild and catalytic procedure for the intramolecular Friedel−Crafts acylation of aromatics with Meldrum's acids. The present protocol has some advantages over the existing methods in term of operational simplicity, preparation, and versatility of the cyclization precursors and 1-indanones. Further research is ongoing to apply this method to other systems and establish the reaction mechanism.

Acknowledgment. The Natural Science and Engineering Research Council of Canada and the University of Waterloo are thanked for financial support. D.F. thanks the Government of Ontario for a fellowship (OGSST). Andrew Martins is acknowledged for preliminary experiments.

Supporting Information Available: Experimental procedures and characterization for compounds **2a**−**f**, **4a**−**g**, **5a**−**e**, **6a**,**b**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) In the absence of $Sc(OTf)_3$, the starting material was quantitatively recovered.