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Meldrum's Acids as Acylating Agents in the Catalytic Intramolecular Friedel−Crafts Reaction

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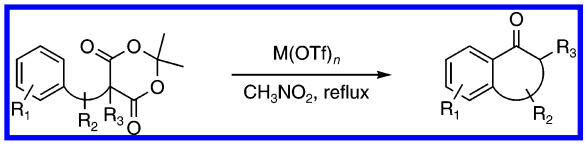

The intramolecular Friedel−Crafts acylation of aromatics with Meldrum's acid derivatives catalyzed by metal trifluoromethanesulfonates is reported. Meldrum's acids are easily prepared, functionalized, handled, and purified. The synthesis of polysubstituted 1-indanones from benzyl Meldrum's acids was investigated thoroughly, and it was shown that a variety of catalysts were effective, while accommodating a diversity of functional groups under mild conditions. The scope, limitations, and functional group tolerance (terminal alkene and alkyne, ketal, dialkyl ether, dialkyl thioether, aryl methyl ether, aryl TIPS and TBDPS ethers, nitrile- and nitro-substituted aryls, alkyl and aryl halides) for a variety of 5-benzyl (enolizable Meldrum's acids) and 5-benzyl-5-substituted Meldrum's acids (quaternized Meldrum's acids), forming 1-indanones and 2-substituted-1-indanones, respectively, are delineated. This method was further applied to the synthesis of 1-tetralones, 1-benzosuberones, and the potent acetylcholinesterase inhibitor donepezil. Rate of cyclization as a function of ring size was established for various benzocyclic ketones via competition experiments: 1-tetralones form faster than both 1-indanones and 1-benzosuberones, and 1-benzosuberones cyclize faster than 1-indanones.

Introduction

The intramolecular Friedel−Crafts acylation is the most powerful carbon−carbon forming reaction in synthetic organic chemistry for the synthesis of benzocyclic ketones, which comprise 1-indanones, 1-tetralones, 1-benzosuberones, and related compounds.[1] These structural motifs have proven synthetic utility in numerous biologically active natural products[2] and play a major role in medicinal chemistry and the development of pharmaceuticals.[3] As illustrated in Figure 1, the antihypertensive drug (+)-indacrinone,[4] the norditerpene taiwaniaquinol B,[5] and the acetylcholinesterase inhibitor

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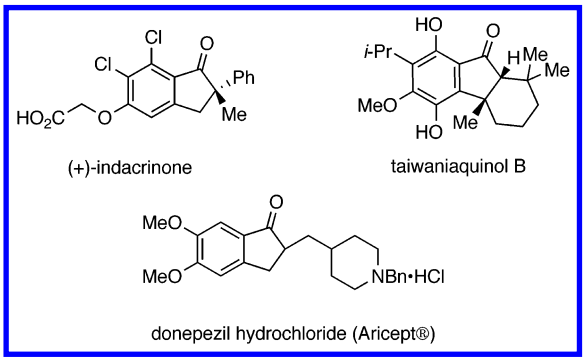

FIGURE 1. Bioactive 1-indanones

donepezil hydrochloride (Aricept),[6] used for the treatment of Alzheimer's disease, all contain a 1-indanone core.[7]

Conditions for the mild and catalytic acylation of aromatic compounds with broad functional group tolerance have been elusive. Existing procedures work well with simple substrates but are rarely applicable to functionalized precursors. The classical intramolecular Friedel–Crafts acylation involves the reaction of an acyl halide or carboxylic acid with a tethered arene promoted by either Lewis or Brønsted acids.[8] Reacting an aromatic with an acyl chloride in combination with a strong Lewis acid such as $AlCl_3$, $TiCl_4$, or $SnCl_4$ is one of the most common acylation procedures. However, due to catalyst inhibition by the product, via formation of a stable Lewis acid–aromatic ketone complex, stoichiometric or excess amounts of the oxophilic promoter are necessary. Furthermore, decomposition of this complex by aqueous workup renders product isolation tedious. Additional drawbacks of this protocol include the moisture sensitivity of acyl chlorides and the generation of hydrogen chloride. Alternatively, the reaction of acyl chlorides with stoichiometric quantities of trifluromethanesulfonic acid provides good yields of benzocyclic ketones via highly reactive sulfocarboxylic acid anhydride intermediates.[9] Lewis acid-catalyzed intramolecular Friedel–Crafts acylation procedures with acyl halides have not been reported.[10]

Complementary intramolecular acylation methods that directly use carboxylic acids as the electrophile suffer from the poor leaving group ability of the –OH moiety and thus require forcing conditions. Friedel–Crafts dehydrative acylation with carboxylic acids have been promoted by polyphosphoric acid,[11] methanesulfonic acid, HF, or dehydrating agents such as P_2O_5, trifluoroacetic anhydride, and trifluoromethanesulfonic anhydride.[8] Nafion-H, an immobilized perfluorinated sulfonic acid, does not form stable complexes with aryl ketones in the acylation with acyl chlorides or carboxylic acids.[12] Although Nafion-H has been reported to effectively promote intramolecular dehydrative Friedel–Crafts acylations to yield tetralones at moderate temperature, it was ineffective for preparing the synthetically more challenging indanones. Generally, 1-tetralones are the easiest benzocyclic ketones to form by intramolecular Friedel–Crafts acylation. Difficulties are associated with 1-indanone synthesis and rigorous conditions are typically required for their preparation, including high temperatures and long reaction times.[13]

The synthetic importance of the Friedel–Crafts acylation has generated interest in the development of a catalytic version under mild reaction conditions. Progress has been made toward intermolecular Lewis acid-catalyzed protocols with use of rare-earth metal triflates but cyclization precursors are still essentially limited to acid halides and anhydrides.[14] The intermolecular acylation of aromatics with carboxylic acids at moderate temperature by the combined use of perfluoroalkanoic acid anhydride and $Bi(OTf)_3$ or $Sc(OTf)_3$, via the in situ generation of an anhydride intermediate, was described.[15,16] Dehydrative cyclization protocols catalyzed by $Bi(NTf_2)_3$ and $Tb(OTf)_3$ were reported, but elevated temperatures were required, between 180 and 200 °C for the synthesis of 1-tetralones[17] and 250 °C for the preparation of 1-indanones.[18,19]

Rather than examining reaction conditions, little attention has been paid to the elaboration of novel acylating agents. Operationally simple intramolecular Friedel–

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Crafts reactions would be facilitated by the availability of a moisture-stable, highly electrophilic precursor[20] that is easily prepared, functionalized, and purified, preferably by recrystallization. Such a precursor should ideally provide aromatic ketones catalytically at moderate temperatures while generating only volatile and inert side products. This acylating agent should be sufficiently flexible for the facile and expedient modification and assembly of diverse polycyclic ring systems.

Ketenes,[21] isocyanates,[22] isothiocyanates,[23] β-lactams,[24] cyclic anhydrides,[25] azalactones,[26] carbamates,[27] and nitriles[28] have been exploited as electrophiles in intramolecular Friedel−Crafts acylations but with limited success and/or lack of generality. Esters and lactones have attracted little attention as acylating agents due to the predominant Friedel−Crafts alkylation pathway,[29] the carboxylate being an excellent leaving group when activated by a Lewis acid.[30] A survey of the literature on intramolecular Lewis acid-promoted Friedel−Crafts acylation with esters provided two examples.[31] Pinnick and co-workers reported a tandem Friedel−Crafts alkylation/acylation of benzene with ethyl cyclopropanecarboxylate promoted by excess $AlCl_3$ at 80 °C to yield 2-methyl-1-indanone in 93% yield.[32] Gewald's group described the formation of 4-oxo-3-(1,4-dihydro-3-cinnoline)carbonitrile in 64% yield from ethyl 2-cyano-2-(2-phenylhydrazono)-acetate and excess $AlCl_3$ at reflux in chlorobenzene.[33]

In our hands, the application of Pinnick's and Gewald's work to a catalytic Friedel−Crafts acylation protocol with esters for the preparation of 1-indanones was unfruitful. The methyl ester **1**,[34] bearing an electron-rich π-nucleophile,[35] was treated with a catalytic amount of $BF_3{\cdot}OEt_2$. The formation of indanone **2** with only 10% conversion directly reflected the quantity of Lewis acid used and the stoichiometric nature of the process (Scheme 1). Since the primary objective was to devise a catalytic acylation reaction, metal trifluoromethanesulfonate catalysts were examined. Ester **1** was treated with $Mg(OTf)_2$ but the starting material was quantitatively recovered after 24 h at reflux in CH_3NO_2. Mono- and dialkylated malonates **3**[36] and **4** were inert in the presence of $Sc(OTf)_3$, and it was therefore concluded that methyl esters held little promise in metal-catalyzed intramolecular Friedel−Crafts acylation reactions. Efforts were then focused on the development of a potent electrophile for these reaction conditions.

Crow and McNab reported that Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) could act as an electrophile in Friedel−Crafts acylation; flash vacuum pyrolysis

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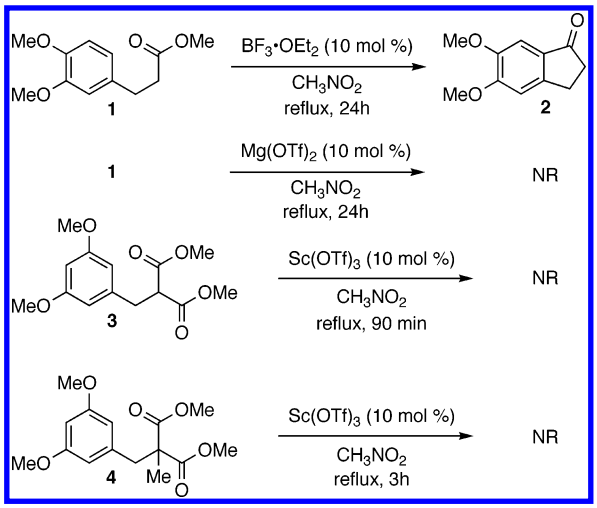
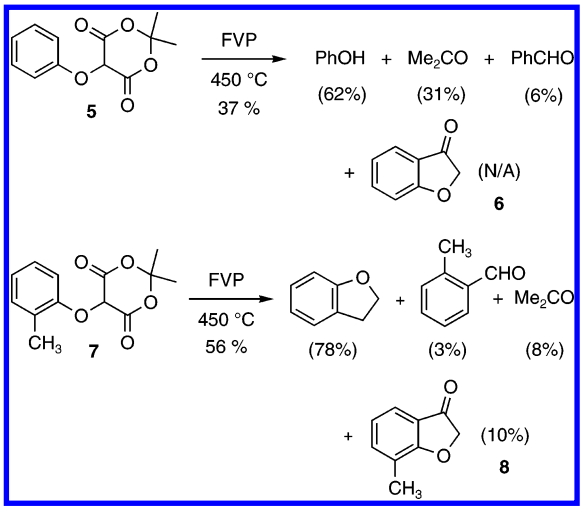
(36) Ke, T.; Wescott, C. R.; Klibanov, A. M. *J. Am. Chem. Soc.* **1996**, *118*, 3366−3374.

SCHEME 1. Intramolecular Friedel–Crafts Acylation with Esters and Malonates



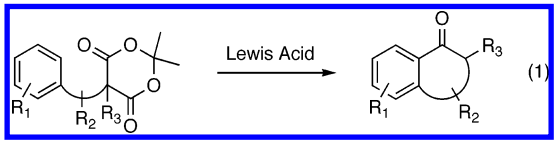
(FVP) of 2,2-dimethyl-5-phenoxy-1,3-dioxan-4,6-dione (**5**) at 450 °C yielded benzofuran-2(3*H*)-one (**6**) in an undetermined (N/A) yield (Scheme 2).[37] Starting from the analogous toluyl derivative **7**, a 6% yield of the Friedel–Crafts acylation product **8** was obtained and the authors proposed that the acylation proceeded via the intermediacy of a phenoxyketene.

SCHEME 2. FVP of Meldrum's Acid Derivatives



Other than McNab's work, the addition of carbon-based nucleophiles to Meldrum's acid derivatives has not been exploited.[38] The high acidity of Meldrum's acid and its propensity to enolize in the presence of weak Brønsted or Lewis bases complicate nucleophilic addition to its highly electrophilic carbonyl groups. It was considered that neutral nonbasic π-nucleophiles would add to Meldrum's acid derivatives in the presence of a Lewis acid to further activate the carbonyl groups.[39] Recent work from our laboratories has demonstrated that Meldrum's acid derivatives are indeed effective acylating agents in intramolecular Friedel–Crafts reactions catalyzed by $Sc(OTf)_3$ under mild reaction conditions.[40] Meldrum's acid is a versatile reagent, which offers several advantages over the conventional electrophiles: the precursors are readily prepared by mono- and difunctionalization at the 5-position,[41] easily purified, and frequently crystalline. Meldrum's acids are highly stable with a long shelf life at room temperature. In addition, volatile byproducts, namely carbon dioxide and acetone, are generated in the acylation process.

We report herein the full account of our findings on the intramolecular Friedel–Crafts acylation of aromatics with Meldrum's acid derivatives catalyzed by metal trifluoromethanesulfonates under mild reaction conditions (eq 1). The preparation of polysubstituted 1-indanones from benzyl Meldrum's acids was investigated thoroughly, and it was shown that a diversity of catalysts can promote the reaction and many functional groups are tolerated by these relatively mild conditions in comparison to conventional methods. The scope, limitations, and functional group tolerance for a variety of 5-benzyl (enolizable Meldrum's acids) and 5-benzyl-5-substituted Meldrum's acids (quaternized Meldrum's acids), forming 1-indanones and 2-substituted-1-indanones, respectively, in good to excellent yields, are delineated. This method was further applied to the synthesis of 1-tetralones, 1-benzosuberones, and the acetylcholinesterase inhibitor donepezil.



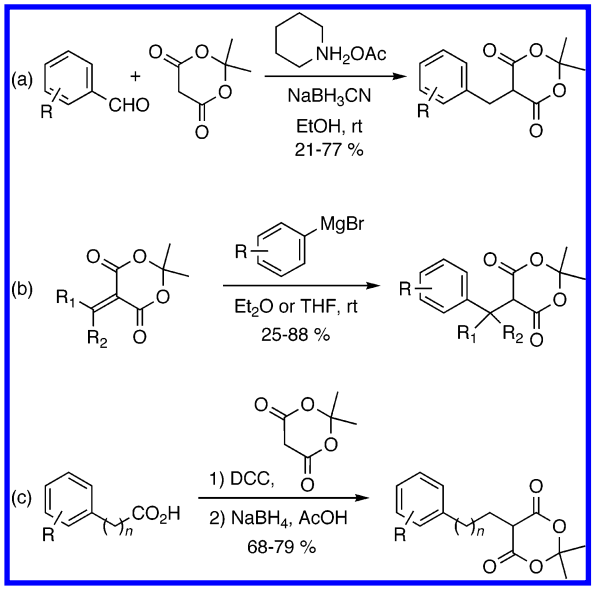
Results and Discussion

Substrate Preparation. To examine the proposed methodology of catalytic Friedel–Crafts acylation with Meldrum's acid derivatives, a ready supply of substrates with appropriately tethered aromatics was required. Meldrum's acid is a poor nucleophile, yet has a high propensity to overalkylate at the 5-position. Several approaches were therefore used to access substrates with variable tether length and substituents within both the aromatic and aliphatic portions of the molecule (Schemes 3 and 4). 5-Benzyl Meldrum's acids unsubstituted at the benzylic position were procured on large scale by reductive alkylation of Meldrum's acid with benzaldehydes. Reductive alkylation methods, which proceed via a tandem Knoevenagel condensation/alkylidene reduction, were previously reported in the literature with sodium hydrogen telluride,[42] borane·dimethylamine complex,[43] and triethylammonium formate[44] as the reducing agents.[45]

(37) Crow, W. D.; McNab, H. *Aust. J. Chem.* **1979**, *32*, 111–121.
(38) For a review on the FVP of Meldrum's acid derivatives, see: (a) Gaber, A. E.-A. O.; McNab, H. *Synthesis* **2001**, 2059–2074. (b) Mahidol, C.; Pinyopronpanit, Y.; Radviroongit, S.; Thebtaranonth, C.; Thebtaranonth, Y. *J. Chem. Soc., Chem. Commun.* **1998**, 1382–1383.
(39) Few examples of Meldrum's acid derivatives activation by Lewis acids have been reported, see: (a) Renslo, A. R.; Danheiser, R. L. *J. Org. Chem.* **1998**, *63*, 7840–7850. (b) Rigo, B.; Fasseur, D.; Cauliez, P.; Couturier, D. *Tetrahedron Lett.* **1989**, *30*, 3073–3076.
(40) For a communication of our initial work, see: Fillion, E.; Fishlock, D. *Org. Lett.* **2003**, *5*, 4653–4656.
(41) (a) Chen, B.-C. *Heterocycles* **1991**, *32*, 529–597. (b) McNab, H. *Chem. Soc. Rev.* **1978**, *7*, 345–358.
(42) Huang, X.; Xie, L. *Synth. Commun.* **1986**, *16*, 1701–1707.
(43) Hrubowchak, D. M.; Smith, F. X. *Tetrahedron Lett.* **1983**, *24*, 4951–4954.
(44) Tóth, G.; Kövér, K. E. *Synth. Commun.* **1995**, *25*, 3067–3074.
(45) For a two-step protocol, see: Wright, A. D.; Haslego, M. L.; Smith, F. X. *Tetrahedron Lett.* **1979**, *20*, 2325–2326.

5-Alkyl Meldrum's acids have been prepared by reducing isopropylidene acylmalonates, via the intermediacy of an alkylidene, with either $NaBH_3CN$ or $NaBH_4$ in AcOH.[46,47] It was believed that these reported protocols could be combined such that the condensation/reduction sequence could be conveniently executed in one pot by using $NaBH_3CN$ in a buffered medium.[48] Indeed, benzyl Meldrum's acids were successfully prepared from substituted benzaldehydes and Meldrum's acid with $NaBH_3CN$ at room temperature in the presence of a catalytic amount of piperidinium acetate in EtOH. In most cases, the highly crystalline products were purified, for convenience and practicality, by recrystallization from MeOH or EtOH.

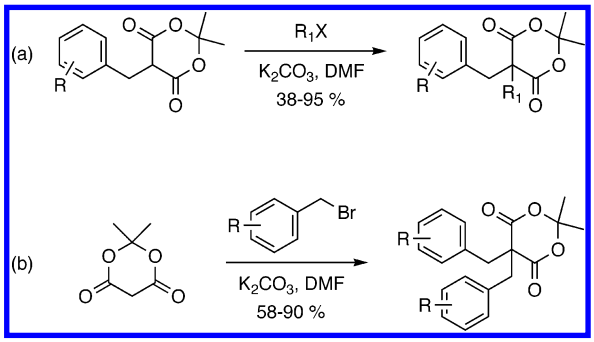
SCHEME 3. 5-Monosubstituted Meldrum's Acid Synthesis



5-Benzyl Meldrum's acid derivatives mono- and disubstituted at the benzylic position were accessed via 1,4-conjugate addition of aryl Grignard's to Meldrum's alkylidenes following literature procedures.[49,50] Disubstituted Meldrum's alkylidenes were prepared by Knoevenagel condensation of Meldrum's acid with ketones (cyclohexanone, tetrahydro-4*H*-pyran-4-one, tetrahydrothiopyran-4-one, acetone) in pyridine in the presence of a catalytic amount of piperidine[51] or molecular sieves,[49a] or via dehydrative condensation with $TiCl_4$ in CH_2Cl_2.[52] The alkylidenes were unstable on silica gel and purified by recrystallization from MeOH or EtOH. These cyclization precursors could also be obtained by conjugate addition of alkyl and aryl Grignard's or dialkylaluminum reagents[53] to Meldrum's acid arylidenes. The arylidenes were obtained by the condensation of Meldrum's acid with benzaldehydes in water,[54] or by the addition of aryl Grignards to methoxymethylene Meldrum's acid.

Substrates with longer tether length (5-ethylbenzyl and 5-propylbenzyl) were synthesized by using Tsukamoto's methodology. Carboxylic acids were coupled to Meldrum's acid with use of DCC to form the isopropylidene acylmalonates that were subsequently reduced with $NaBH_4$ in AcOH to the corresponding 5-alkyl Meldrum's acids.[47]

SCHEME 4. 5,5-Disubstituted Meldrum's Acid Synthesis



Symmetrical 5,5-dibenzyl substrates were prepared in one step by reacting Medrum's acid with 2 equivalents of the appropriate benzyl bromide, using K_2CO_3 in DMF (Scheme 4).[55] Unsymmetrical 5-benzyl-5-substituted Meldrum's acids were produced from monosubstituted substrates in an analogous manner, by alkylation with iodomethane, allyl bromide, propargyl bromide, and various benzyl bromides.[56] Quaternized Meldrum's acids were easily isolated in an analytically pure form by extraction and further purified by recrystallization from MeOH.

Friedel–Crafts Acylation with Enolizable Meldrum's Acids. To study the viability of the proposed intramolecular Friedel–Crafts strategy, substrate **9** bearing an electron-rich π-nucleophile was selected as the initial and optimal cyclization precursor. Various reaction conditions, Lewis acids ($Sc(OTf)_3$, $Dy(OTf)_3$, $Yb(OTf)_3$, and

(46) (a) Rosowsky, A.; Forsch, R.; Uren, J.; Wick, M.; Kumar, A. A.; Freisheim, J. H. *J. Med. Chem.* **1983**, *26*, 1719–1724. (b) Nutaitis, C. F.; Schultz, R. A.; Obaza, J.; Smith, F. X. *J. Org. Chem.* **1980**, *45*, 4606–4608.

(47) (a) Hin, B.; Majer, P.; Tsukamoto, T. *J. Org. Chem.* **2002**, *67*, 7365–7368. (b) Smrcina, M.; Majer, P.; Majerova, E.; Guerassina, T. A.; Eissenstat, M. A. *Tetrahedron* **1997**, *53*, 12867–12874.

(48) Following our initial publication,[40] a one-pot reductive alkylation of Meldrum's acid with benzaldehydes using $NaBH_4$ was reported, see: Desai, U. V.; Pore, D. M.; Mane, R. B.; Solabannavar, S. B.; Wadgaonkar, P. P. *Synth. Commun.* **2004**, *34*, 25–32.

(49) (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. (g) For the enantioselective addition of Et_2Zn, see: Watanabe, T.; Knöpfel, T. F.; Carreira, E. M. *Org. Lett.* **2003**, *5*, 4557–4558.

(50) Generally, copper catalysis was not required.

(51) (a) Baty, J. D.; Jones, G.; Moore, C. *J. Org. Chem.* **1969**, *34*, 3295–3302. (b) For the synthesis of methyl alkylidene Meldrum's acid, see: Ziegler, F. E.; Guenther, T.; Nelson, R. V. *Synth. Commun.* **1980**, *10*, 661–665.

(52) Brown, R. F. C.; Coulston, K. J.; Eastwood, F. W.; Gatehouse, B. M.; Guddatt, L. W.; Luke, W.; Pfenninger, M.; Rainbow, I. *Aust. J. Chem.* **1984**, *37*, 2509–2524.

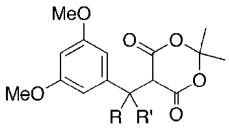
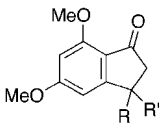
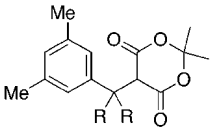
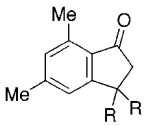
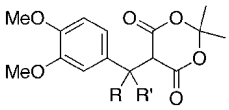
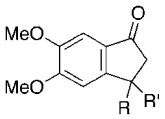
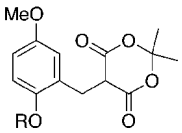
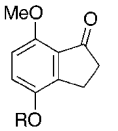
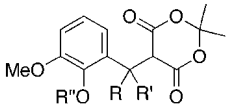
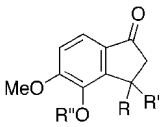
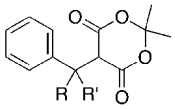
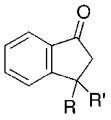
(53) Maas, S.; Stamm, A.; Kunz, H. *Synthesis* **1999**, 1792–1798.

(54) Bigi, F.; Carloni, S.; Ferrari, L.; Maggi, R.; Mazzacani, A.; Sartori, G. *Tetrahedron Lett.* **2001**, *42*, 5203–5205.

(55) (a) Desai, D. G.; Mane, R. B. *Chem. Ind.* (*London*) **1982**, 809. For alternative methods, see: (b) Dhuru, S. P.; Mohe, N. U.; Salunkhe, M. M. *Synth. Commun.* **2001**, *31*, 3653–3657. (c) Shing, T. K. M.; Li, L.-H.; Narkunan, K. *J. Org. Chem.* **1997**, *62*, 1617–1622. (d) Chen, B.-C.; Lue, P. *Org. Prep. Proc. Int.* **1992**, *24*, 185–188.

(56) Mane, R.; Krishna Rao, G. S. *Chem. Ind.* (*London*) **1976**, 786–787.

TABLE 1. Intramolecular Friedel–Crafts Acylation with Enolizable Benzyl Meldrum's Acids

entry	Meldrum's acid substrate	$M(OTf)_n$	loading (mol %)	time (min)	indanone	yield (%)
						
1	**9**, R = R' = H	$Sc(OTf)_3$	12	60	**10**, R = R' = H	73[a]
2	**9**, R = R' = H	$Dy(OTf)_3$	12	60	**10**, R = R' = H	56
3	**9**, R = R' = H	$Yb(OTf)_3$	12	60	**10**, R = R' = H	67
4	**9**, R = R' = H	—	—	360	**10**, R = R' = H	55[b]
5	**11**, R = H; R' = Me	$Sc(OTf)_3$	12	120	**12**, R = H; R' = Me	77[c]
6	**13**, R = R' = Me	$Sc(OTf)_3$	12	120	**14**, R = R' = Me	82[c]
7	**15**, R = R' = $-(CH_2)_5-$	$Sc(OTf)_3$	12	120	**16**, R = R' = $-(CH_2)_5-$	83[c]
8	**17**, R = R' = $-(CH_2)_2O$	$Sc(OTf)_3$	10	15	**18**, R = R' = $-(CH_2)_2O$	N/A
9	**17**, R = R' = $-(CH_2)_2O$	$Yb(OTf)_3$	10	15	**18**, R = R' = $-(CH_2)_2O$	79
10	**19**, R = R' = $-(CH_2)_2S$	$Yb(OTf)_3$	8	20	**20**, R = R' = $-(CH_2)_2S$	86
11	**21**, R = R' = $-(CH_2)_2C(OCH_2)_2$	$Yb(OTf)_3$	7	1260 (21 h)	**22**, R = R' = $-(CH_2)_2C(OCH_2)_2$	78[d]
						
12	**23**, R = H	$Sc(OTf)_3$	12	560	**24**, R = H	52[e]
13	**25**, R = $-(CH_2)_5-$	$Sc(OTf)_3$	12	90	**26**, R = $-(CH_2)_5-$	75[f]
						
14	**27**, R = R' = H	$Sc(OTf)_3$	10	45	**2**, R = R' = H	59
15	**28**, R = H; R' = Me	$Sc(OTf)_3$	10	20	**29**, R = H; R' = Me	68
16	**30**, R = R' = Me	$Sc(OTf)_3$	9	20	**31**, R = R' = Me	69
						
17	**32**, R = Me	$Sc(OTf)_3$	10	20	**33**, R = Me	32
18	**34**, R = TBDPS	$Sc(OTf)_3$	10	35	**35**, R = TBDPS	63
						
19	**36**, R = R' = H; R'' = Me	$Sc(OTf)_3$	9	80	**37**, R = R' = H; R'' = Me	64
20	**38**, R = H; R' = R'' = Me	$Sc(OTf)_3$	10	40	**39**, R = H; R' = R'' = Me	38
21	**40**, R = R' = R'' = Me	$Sc(OTf)_3$	10	35	**41**, R = R' = R'' = Me	N/A
22	**42**, R = R' = H; R'' = TBDPS	$Sc(OTf)_3$	10	40	**43**, R = R' = H; R'' = TBDPS	50
23	**44**, R = R' = H; R'' = TIPS	$Sc(OTf)_3$	13	40	**45**, R = R' = H; R'' = TIPS	45
						
24	**46**, R = R' = H	$Sc(OTf)_3$	12	540	**47**, R = R' = H	13[g]
25	**48**, R = R' = $-(CH_2)_5-$	$Sc(OTf)_3$	12	30	**49**, R = R' = $-(CH_2)_5-$	56[h]
26	**50**, R = Me; R' = $-(CH_2)_5Cl$	$Sc(OTf)_3$	10	15	**51**, R = Me; R' = $-(CH_2)_5Cl$	52

[a] A 68% yield was obtained in CH_3CN (2 h, 8 mol % catalyst), and a 72% yield in 1,2-dichloroethane (4.5 h, 12 mol % catalyst). [b] 90% conversion. [c] The reaction was run in CH_3CN. [d] Powdered 5 Å MS (100 wt %) were added to the reaction mixture. [e] The substrate was added by syringe pump, over approximately 8 h, to a refluxing solution of $Sc(OTf)_3$, followed by an additional ~1 at reflux. The one-pot procedure yielded the indanone in 36% yield. [f] The slow addition protocol furnished the indanone in 73%. [g] The one-pot procedure failed to produce 1-indanone. [h] A yield of 57% was obtained when the slow addition procedure was used.

TMSOTf), Brønsted acids (TfOH and TFA), and solvents were investigated. Optimal yields for the formation of 5,7-dimethoxy-1-indanone (**10**) were obtained when the acylation was catalyzed by $Sc(OTf)_3$ (Table 1, entry 1). Refluxing nitromethane, acetonitrile, and 1,2-dichloroethane provided comparable yields but with variable

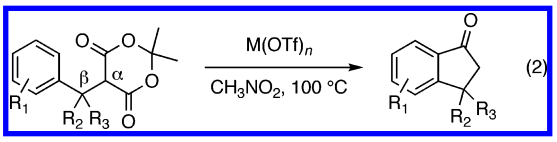
reaction times. Short reaction times motivated the use of nitromethane as the standard solvent.

$Yb(OTf)_3$ and $Dy(OTf)_3$ provided indanone **10** in lower yields (Table 1, entries 2 and 3) compared to $Sc(OTf)_3$, even though TLC and ^1H NMR analysis of the crude reaction mixtures revealed clean material that could be easily purified by flash chromatography. When the acylation was conducted with 20 mol % of TMSOTf, TFA, or TfOH in refluxing 1,2-dichloroethane, a 60%, 37%, and 38% yield was obtained, respectively. Furthermore, complex mixtures of products were formed that made the indanone purification tedious. It is noteworthy that the electrophilic substitution proceeded in the absence of a catalyst within 6 h in refluxing CH_3NO_2 to yield indanone **10** in 55% yield (Table 1, entry 4), consistent with thermal decomposition of 5-monosubstituted Meldrum's acid derivatives.[57] Purification of indanone **10**, generated thermally, was difficult due to the formation of numerous byproducts of similar polarity.

Considering the thermal instability of Meldrum's acids and the potential background reaction, the development of a protocol requiring short reaction times would minimize side reactions. A typical acylation reaction was conducted by simple combination of the substrate, dried $Sc(OTf)_3$, and distilled nitromethane in a round-bottom flask equipped with a reflux condenser. The resulting suspension was immediately immersed in an oil bath preheated to 100 °C and consumption of the starting material was monitored by TLC. For practicality, no aqueous workup was performed, and nitromethane was removed under vacuum and the residue was purified by flash chromatography on silica gel.

A stoichiometric amount of acetone is produced in the Friedel−Crafts acylation with Meldrum's acids. To ascertain whether acylation yields were affected by side reactions between the 1-indanones and acetone, a control experiment was conducted with equimolar amounts of 1-indanone (**47**) and acetone with a catalytic quantity of $Sc(OTf)_3$ in refluxing nitromethane. GC-MS and ^1H NMR analysis of the crude reaction mixture showed no decomposition of the indanone, nor any formation of aldol products.

The scope of the intramolecular Friedel−Crafts acylation of 5-benzyl Meldrum's acids has been fully defined by varying the pattern of substitution and electron-donating ability of the π-nucleophile unit, as well as substitution at the β-position (in the tether) to generate a diversity of functionalized 1-indanones in yields ranging from 13% to 86% (eq 2). The results are compiled in Table 1.



Mixed results were obtained for the acylation with enolizable Meldrum's acids. The electron-rich 3,5-dimethoxybenzyl Meldrum's acid substrates (entries 1−11) provided good yields (73−86%) of 1-indanones, while yields were modestly lower (13−75%) with the less electron-rich π-nucleophiles (3,5-dimethylbenzyl, 3,4-dimethoxybenzyl, 2,5-dimethoxybenzyl, 2,3-dimethoxybenzyl, and benzyl).

Slow addition of the substrate over approximately 8 h with a syringe pump to a suspension of $Sc(OTf)_3$ in nitromethane at 100 °C improved the acylation yield. 3,5-Dimethylbenzyl Meldrum's acid (**23**) afforded indanone **24** in a 36% yield with use of the standard protocol described above, yet the yield was increased to 52% via the slow addition technique (Table 1, entry 12).

The introduction of substituents at the benzylic position (β-position) had a profound influence upon the ease of acylation. Increased substitution slightly improved the efficiency of the acylation reaction for the electron-rich 3,5-dimethoxybenzyl and 3,4-dimethoxybenzyl Meldrum's acid substrates (entries 5−7 and entries 14−16). Substantial yield enhancements were observed for cyclization precursors bearing a weak π-nucleophile like 3,5-dimethylbenzyl Meldrum's acid substrate **25** and benzyl Meldrum's acids **48** and **50** (Table 1, entries 13, 25, and 26). For the latter, the acylations were reasonably efficient and, for comparison, Meldrum's acid **46** did not provide 1-indanone (**47**) under the same reaction conditions (entry 24). The slow addition procedure failed to increase the yield when the β-position was substituted.

Acylation of substrate **38**, with a methyl benzylic substitutent, provided a low yield of indanone **39** in 38% (Table 1, entry 20). The disubstituted substrate **40** produced only an intractable mixture of decomposition products. This surprising trend reversal (Table 1, entries 19−21) may be attributable to the unusual conformation adopted by these substrates compared with the other series of β-substituted Meldrum's acids. It is speculated that the conformation adopted by these substrates is unusual compared to other series of (β-substituted)benzyl Meldrum's acids. That conformational difference is apparent from the remarkable chemical shift of the acidic hydrogen of Meldrum's acid (the proton at the 5-position). The chemical shift is 5.38 ppm for compound **40**, in comparison to 3.46 and 3.59 ppm respectively for the analogous 3,4-dimethoxybenzyl and 3,5-dimethoxybenzyl Meldrum's acids **30** and **13**. This chemical shift discrepancy is not seen with monomethyl substate **38**, despite the lower acylation yield. Severe steric interactions between the methyl substituents at the β-position and the methoxy group at the 2-position of the aromatics can be invoked.

A significant number of cases are described in the literature where intramolecular acylation of aryl ethers has proven difficult in the formation of 1-indanones.[58] Particularly challenging is the acylation of aromatics substituted with a methoxy group meta to the site of the electrophilic substitution, in which the methoxy inductively deactivates the π-nucleophile. Such a scenario is found in the 3,4-dimethoxybenzyl, 2,5-dimethoxybenzyl, and 2,3-dimethoxybenzyl Meldrum's acids. Despite the presence of an ortho (Table 1, entries 17 and 18) or para directing methoxy group (Table 1, entries 14−16 and 19−

(57) At temperatures above 100 °C, Meldrum's acid derivatives tautomerize to the corresponding 6-hydroxydioxinones that further undergo retro-Diels−Alder reaction to furnish acylketenes. (a) For a review, see: Sato, M.; Iwamoto, K. *J. Synth. Org. Chem. Jpn.* **1999**, *57*, 76−83. (b) Sato, M.; Ban, H.; Kaneko, C. *Tetrahedron Lett.* **1997**, *38*, 6689−6692. (c) Matoba, K.; Yamazaki, T. *Chem. Pharm. Bull.* **1983**, *31*, 2955−2956. (d) Bihlmayer, G. A.; Schuster, P.; Polansky, O. E. *Monatsh. Chem.* **1966**, *97*, 145−149.

(58) Buckley, T. F., III; Rapoport, H. *J. Am. Chem. Soc.* **1980**, *102*, 3056−3062 and references therein.

21), the overall π-nuclophilicity of the arene was reduced by the meta methoxy substituent and diminished the efficiency of the cyclization. The acylation of the 3,4-dimethoxybenzyl substrates **27**, **28**, and **30** was regioselective (Table 1, entries 14−16) and analysis of the crude mixtures by ^{1}H NMR and GC-MS showed the exclusive formation of 5,6-dimethoxy-1-indanones.

Functional Group Compatibility. A wide range of functional groups was compatible with this Friedel−Crafts acylation methodology. Accompanying aryl methyl ether cleavage by the Lewis acid catalyst has been observed previously in Friedel−Crafts acylation with use of the classical electrophiles and reaction conditions.[58,59] This protocol was mild enough to not induce dealkylation of aryl methyl ether ortho and para to the newly introduced acyl group (Table 1, entries 1−11 and 14−23). In addition, dialkyl ethers (Table 1, entry 9) and aryl TBDPS and TIPS ethers (Table 1, entries 18, 22, and 23) were accommodated, but the reaction conditions were fine-tuned in some cases. For instance, the Lewis basic cyclic ether **17**, when treated with $Sc(OTf)_3$, yielded a trace amount of indanone **18** but substantial decomposition was also observed (Table 1, entry 8). Gratifyingly, spiro-indanone **18** was formed in 79% yield with $Yb(OTf)_3$ (Table 1, entry 9). A similar result was obtained for the cyclization of dialkyl thioether **19** (Table 1, entry 10).

The superior mildness of this Friedel−Crafts acylation protocol is illustrated by its compatibility with acid-labile 1,3-dioxolane. Submitting substrate **21** to the standard reaction conditions with use of $Sc(OTf)_3$ gave a 40% yield, after 20 min, of a 1.9:1 mixture of ketal:ketone. The use of catalytic $Dy(OTf)_3$, $Yb(OTf)_3$, or $BF_3{\cdot}OEt_2$ improved substantially the acylation efficiency (77% (2.5:1), 75% (2.9:1), and 75% (1.7:1), respectively) but unsatisfactory deprotection was still observed. Running the acylation with a protic acid scavenger, DTBMP (1 mol %), did not ameliorate the ratio of ketal to ketone, and furthermore, a low conversion was obtained. $Mg(OTf)_2$ furnished promising results after 5 h, giving an inseparable 5.5:1 mixture of 1,3-dioxolane:ketone, in 45% yield. Despite rigorously drying the catalyst, substrate, and solvent, the presence of water in the reaction mixture was still suspected, and responsible for the cleavage of the 1,3-dioxolane. It was finally found that addition of powdered 5 Å molecular sieves, along with catalytic $Yb(OTf)_3$, gave a 78% yield of indanone **22** in 21 h.[60] Analysis of the crude ^{1}H NMR showed a 28:1 ratio of 1,3-dioxolane:ketone.

It was anticipated that acylation of 2-trialkylsilyloxy substrates **34**, **42**, and **44** would be problematic and could lead to the formation of 2-chromanones (Table 1, entries 18, 22, and 23). Aryltrimethylsilyl ethers have been shown to efficiently add to Meldrum's acid at room temperature to produce monofunctionalized malonic silyl esters.[39b] In contrast to this reported reactivity of aryltrimethylsilyl ethers, aryl TIPS and TBDPS ethers were tolerated by the Friedel−Crafts protocol and lactonization was not observed.

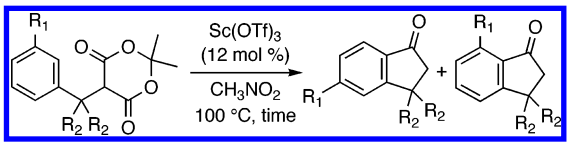
(59) Coburn, C. E.; Anderson, D. K.; Swenton, J. S. *J. Org. Chem.* **1983**, *48*, 1455−1461.

(60) (a) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922−1925. (b) 5 Å Molecular sieves were found not to catalyze the acylation reaction.

Alkyl chlorides were also compatible. Meldrum's acid **50** gave indanone **51** in 52% yield (Table 1, entry 26). This observed reactivity is consistent with that of other unsubstituted benzyl π-nucleophiles. Alkyl halides are useful for further functionalization of the benzocyclic ketones and cannot be directly obtained by using classical Friedel−Crafts conditions.

Regioselectivity of the Friedel−Crafts Acylation with Enolizable Meldrum's Acids. Having established the reactivity of Meldrum's acid derivatives with disubstituted and unsubstituted π-nucleophiles with metal triflate catalysis, the acylation protocol was applied to meta-substituted aromatics and the regioselectivity of the process determined. As discussed earlier, the importance of substitution at the benzylic position was prominent for substrates bearing a weak π-nucleophilic moiety (Table 2). Regioisomeric indanones were obtained from 3-methoxybenzyl and 3-methylbenzyl Meldrum's acids (Table 2, entries 1−4) in ratios comparable to classical Friedel−Crafts protocols.[61]

TABLE 2. Friedel−Crafts Acylation of (3-Substituted)benzyl Meldrum's Acids

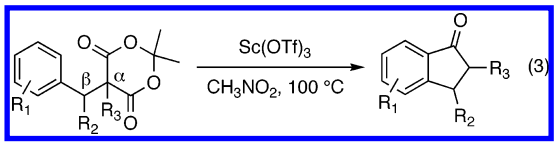


entry	substrate	reaction time (h)	products (para:ortho)[a]	yield (%)
1	**52**, R_1 = OMe; R_2 = H	1	**53:54** (5.5:1)	52
2	**55**, R_1 = OMe; R_2 = $-(CH_2)_5-$	2	**56:57** (3.4:1)	71
3	**58**, R_1 = Me; R_2 = H	1	**59:60** (1:1)	48
4	**61**, R_1 = Me; R_2 = $-(CH_2)_5-$	2	**62:63** (1:1)	62
5	**64**, R_1 = Cl; R_2 = H	2		N/A
6	**65**, R_1 = Cl; R_2 = $-(CH_2)_5-$	2	**66:67** (2:1)	62

[a] Ratio determined by analysis of the crude ^{1}H NMR.

Interestingly, the deactivated 3-chlorobenzyl Meldrum's acid substrate **65** provided a mixture of indanones **66** and **67** in 62% yield (Table 2, entry 6). Cyclization of the analogous substrate **64** unsubstituted at the benzylic position failed (Table 2, entry 5).

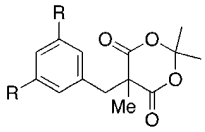
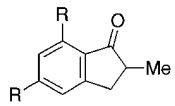
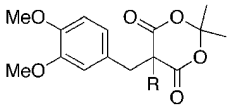
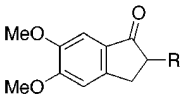
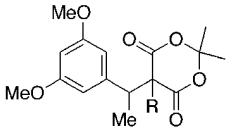
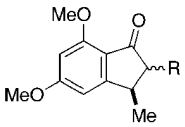
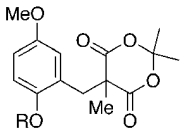
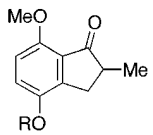
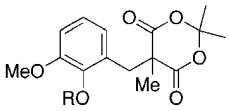
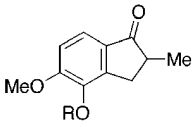
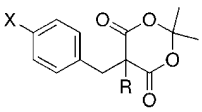
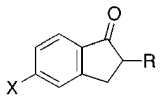
Influence of Substitution at the α-Position of Meldrum's Acids: Intramolecular Friedel−Crafts Acylation with Quaternized Benzyl Meldrum's Acids. In pursuit of our objective of synthesizing polysubstituted 1-indanones, the influence of substitution at the α-position of Meldrum's acid (C-5) was investigated (eq 3).



The acylation of quaternized Meldrum's acid was conducted with substrate **68**, using the conditions developed for the cyclization of enolizable benzyl Meldrum's acids. Contrary to the enolizable substrates, no cyclization occurred in the absence of a catalyst and the starting

(61) Budhram, R. S.; Palaniswamy, V. A.; Eisenbraun, E. J. *J. Org. Chem.* **1986**, *51*, 1402−1406.

TABLE 3. Quaternized Benzyl Meldrum's Acids in Friedel–Crafts Acylation

entry	Meldrum's acid substrate	catalyst	loading (mol %)	time (min)	indanone	yield (%)
						
1	**68**, R = OMe	$Sc(OTf)_3$	10	45	**69**, R = OMe	80
2	**70**, R = Me	$Sc(OTf)_3$	11	30	**71**, R = Me	87
						
3	**72**, R = Me	$Sc(OTf)_3$	10	45	**73**, R = Me	77
4	**74**, R = Ph	$Sc(OTf)_3$	10	60	**75**, R = Ph	67
5	**76**, R = Bn	$Sc(OTf)_3$	10	45	**77**, R = Bn	80
6	**78**, R = $CH_2C{=}CH_2$	$Sc(OTf)_3$	10	45	**79**, R = $CH_2C{=}CH_2$	76
7	**80**, R = CH_2CCH	$Sc(OTf)_3$	10	45	**81**, R = CH_2CCH	80
8	**82**, R = $CH_2Ph(4\text{-}CN)$	$Sc(OTf)_3$	17	320	**83**, R = $CH_2Ph(4\text{-}CN)$	78[a]
9	**84**, R = $CH_2Ph(4\text{-}NO_2)$	$Sc(OTf)_3$	10	250	**85**, R = $CH_2Ph(4\text{-}NO_2)$	81
10	**86**, R = CH_2PhF_5	$Sc(OTf)_3$	7	85	**87**, R = CH_2PhF_5	80
						
11	**88**, R = Me	$Sc(OTf)_3$	10	155	**89**, R = Me (*trans*:*cis* 5.6:1)[b]	91
12	**90**, R = Bn	$Sc(OTf)_3$	17[c]	1935 (32 h)	**91**, R = Bn (*trans*:*cis* 12.3:1)[b]	92
						
13	**92**, R = Me	$Sc(OTf)_3$	10	20	**93**, R = Me	69
14	**94**, R = TBDPS	$Sc(OTf)_3$	12	20	**95**, R = TBDPS	94
						
15	**96**, R = Me	$Sc(OTf)_3$	9	20	**97**, R = Me	75
16	**98**, R = TBDPS	$Sc(OTf)_3$	9	30	**99**, R = TBDPS	86
17	**100**, R = TIPS	$Sc(OTf)_3$	10	40	**101**, R = TIPS	77
						
18	**102**, R = Bn; X = H	$Sc(OTf)_3$	10	50	**103**, R = Bn; X = H	66
19	**102**, R = Bn; X = H	TfOH	10	50	**103**, R = Bn; X = H	71
20	**104**, R = $CH_2Ph(4\text{-}F)$; X = F	$Sc(OTf)_3$	10	360	**105**, R = $CH_2Ph(4\text{-}F)$; X = F	N/A
21	**106**, R = $CH_2Ph(4\text{-}NO_2)$; X = NO_2	$Sc(OTf)_3$	10	60	**107**, R = $CH_2Ph(4\text{-}NO_2)$; X = NO_2	N/A

[a] A 73% yield was obtained after 550 min when the reaction was run with 11 mol % of catalyst. [b] Determined by analysis of the crude ^1H NMR. [c] The catalyst was added in two portions. The reaction was initially started with 7 mol % of catalyst followed by an additional 10 mol % after 23.5 h.

material was recovered. Intuitively, increased substitution at the position α to the carbonyls was anticipated to result in a decreased reactivity based on steric arguments.[62] The catalytic acylation of **68** furnished smoothly 5,7-dimethoxy-2-methyl-1-indanone (**69**) within 45 min in 80% yield (Table 3, entry 1). The potential efficacy of quaternized Meldrums's acids was confirmed by the high-yielding acylation of 5-methyl-5-(3,5-dimethylbenzyl) Meldrum's acid (**70**). In comparison to the analogous 3,5-dimethylbenzyl Meldrum's acid substrates **23** (Table 1, entry 12), a substantial decrease in reaction time with a markedly increasing yield was observed.

These inquiries on the acylation with quaternized Meldrum's acid identified a direct and convenient entry

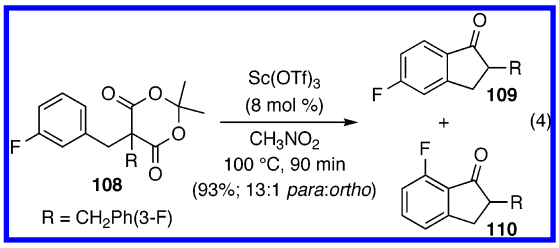
into 2-alkyl-1-indanones. The preparation of this type of medicinally relevant structures usually requires several steps starting from 1-indanones. On the basis of these results, the scope of the intramolecular Friedel−Crafts acylation of quaternized Meldrum's acids was subsequently investigated by varying the pattern of substitution and electron-donating ability of the π-nucleophile moiety, giving access to a diversity of functionalized 2-substituted-1-indanones in yields ranging from 66% to 94% (eq 3).

As shown in Table 3, excellent results were obtained for the Friedel−Crafts acylation with quaternized Meldrum's acids for a variety of substrates. π-Nucleophilicity was not as crucial as for the enolizable substrates and a range of aromatics including 3,4-dimethoxybenzyl, 3,5-dimethoxybenzyl, 2,5-dimethoxybenzyl, and 2,3-dimethoxybenzyl efficiently generated benzocyclic ketones (Table 3, entries 3−10 and 13−17). The benzyl substrate **102** provided a remarkable 66% yield of 2-benzyl-1-indanone (**103**) considering its inability to cyclize in the enolizable series (Table 3, entry 18 versus Table 2, entry 24). In addition to a methyl group, various substituents (allyl, propargyl, aryl, and benzyl) could easily be introduced at the 2-position of the 1-indanones (Table 3, entries 4−10).

A route to 2,3-disubstituted-1-indanones by the C-alkylation of (β-methyl)benzyl Meldrum's acid **11** with iodomethane and benzyl bromide to form substrates **88** and **90**, respectively, was developed. Upon treatment with catalytic $Sc(OTf)_3$, the synthesis of indanones **89** and **91** was achieved as diastereomeric mixtures in greater than 90% yield (Table 3, entries 11 and 12).

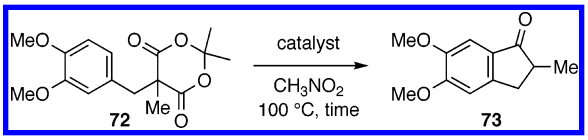
An inherent limitation of this strategy is the inability to C-alkylate (β,β-disubstituted)benzyl Meldrum's acid.[63] Although acylation of these precursors would provide access to 2,3,3-trisubstituted-1-indanones, the generation of two contiguous all-carbon quaternary centers in these substrates was prohibitive.

Friedel−Crafts acylation of the electon-deficient 5,5-di(4-fluorobenzyl) Meldrum's acid (**104**) and the analogous nitro compound **106** failed (Table 4, entries 20 and 21). In both cases, complete decomposition of starting material was observed without providing the desired indanones **105** and **107**. On the other hand, the aromatic substitution of 5,5-di(3-fluorobenzyl) Meldrum's acid (**108**) resulted in a 93% yield of 1-indanones **109** and **110** in a 13:1 regioisomeric mixture in favor of the para product (eq 4).[64]



Optimization of the Lewis Acid Catalyst. The excellent reactivity of quaternized Meldrum's acid systems prompted the reexamination of the reaction conditions initially developed for the acylation of enolizable substrates. To this end, several Lewis acids were surveyed with 5-(3,4-dimethoxybenzyl)-5-methyl Meldrum's acid (**72**). As depicted in Table 4, in addition to $Sc(OTf)_3$, numerous metal trifluoromethanesulfonates (aluminum, magnesium, copper, trimethylsilyl) successfully catalyzed the Friedel−Crafts acylation reaction.[65] Other excellent candidates were TfOH and magnesium bis(trifluoromethanesulfonyl)amide (Table 4, entries 6, and 11). Unexpectedly, $BF_3{\cdot}OEt_2$ was shown to suitably catalyze the acylation reaction (Table 4, entry 10). This first example of $BF_3{\cdot}OEt_2$-catalyzed Friedel−Crafts acylation appears not to suffer from the catalyst inhibition reported for conventional systems.

TABLE 4. Optimization of the Lewis Acid Catalyst



entry	catalyst	loading (mol %)	reaction time (min)	yield (%)
1	$Sc(OTf)_3$	10	20	85
2	$Al(OTf)_3$	10	20	69
3	$Mg(OTf)_2$	10	20	83
4	$Cu(OTf)_2$	10	20	82
5	TMSOTf	10	20	90
6	TfOH	10	20	86
7	LiOTf	10	70	NR
8	KOTf	20−60	90	NR
9	TMSCl	10−35	90	NR
10	$BF_3{\cdot}OEt_2$	10	20	90
11	$Mg(NTf_2)_2$	10	30	84

The Lewis acids TMSCl and $AlCl_3$ were ineffective at promoting the acylation reaction (Table 4, entry 9). The former returned starting material while the latter yielded a trace amount of 1-indanone. With $AlCl_3$, the electrophilic aromatic substitution was sluggish and the main reaction pathway was formation of the acid chloride by the opening of the Meldrum's acid moiety by a chloride ion, following complexation with the carbonyl group. Aqueous workup furnished the corresponding carboxylic acid.

Applying other Lewis acids than $Sc(OTf)_3$ to the dibenzyl Meldrum's acid substrate (**102**) was unproductive. A catalytic amount of $BF_3{\cdot}OEt_2$ led to trace formation of 2-benzyl-1-indanone (**103**) and starting material recovery while $Mg(OTf)_2$ was unable to promote this transformation. From these results, the general superiority of $Sc(OTf)_3$ is obvious, particularly for weak π-nucleophiles. Trifluoromethanesulfonic acid was found to be equally competent (Table 3, entry 19).

(62) Examples of intramolecular electrophilic aromatic substitution with α,α-disubstituted electrophiles, see: (a) Schultz, A. G.; Macielag, M.; Podhorez, D. E.; Suhadolnik, J. C. *J. Org. Chem.* **1988**, *53*, 2456−2464. (b) Newman, H.; Angier, R. B. *J. Org. Chem.* **1966**, *31*, 1456−1461. (c) Eglington, G.; Nevenzel, J. C.; Scott, A. I.; Newman, M. S. *J. Am. Chem. Soc.* **1956**, *78*, 2331−2335. (d) Marvell, E. N.; Geiszler, A. O. *J. Am. Chem. Soc.* **1952**, *74*, 1259−1263.

(63) For C,O-dialkylation of Meldrum's acid, see: Snyder, C. A.; Selegue, J. P.; Dosunmu, E.; Tice, N. C.; Parkin, S. *J. Org. Chem.* **2003**, *68*, 7455−7459.

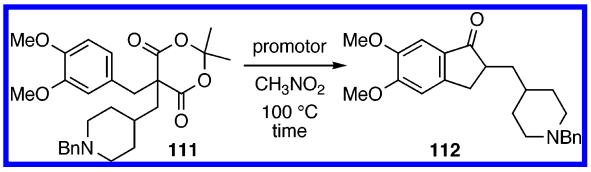
(64) Rosenthal, J.; Schuster, D. I. *J. Chem. Educ.* **2003**, *80*, 679−690.

(65) Olah, G. A.; Farooq, O.; Farnia, S. M. F.; Olah, J. A. *J. Am. Chem. Soc.* **1988**, *110*, 2560−2565.

Intramolecular Friedel–Crafts Acylation with Quaternized Benzyl Meldrum's Acids: Functional Group Tolerance and Application to the Synthesis of Donepezil. Functional group compatibility was consistent with the results obtained in the enolizable Meldrum's acid series. Again, aryl methyl and aryl TBDPS and TIPS ethers were accommodated (Table 3, entries 14, 16, and 17). The mild nature of the Friedel–Crafts acylation process was further demonstrated by reacting substrates containing a terminal alkyne or alkene (Table 3, entries 6 and 7), as well as nitro- and nitrile-substituted aryl groups (Table 3, entries 8 and 9). Prolonged reaction times were required for Lewis basic functional groups, likely due to partial deactivation of the catalyst.

The synthesis of the potent acetylcholinesterase inhibitor donepezil (Figure 1) was tackled, as it contains a tertiary amine within its structure. Attempts at acylating quaternized Meldrum's acid **111** with a catalytic amount of $Sc(OTf)_3$ failed (Table 5, entry 1). It was postulated that the catalyst was inhibited by the Lewis basic tertiary amine,[66] though $Sc(OTf)_3$ has been shown to be an effective catalyst in the presence of basic amines in certain transformations.[67] When substrate **111** was treated with excess $Sc(OTf)_3$, donepezil (**112**) was formed but the yield was undetermined due to its difficult isolation from the reaction mixture (Table 5, entry 2). Donepezil (**112**) was generated smoothly by the reaction of Meldrum's acid **111** with 120 mol % of TfOH in a 61% yield (Table 5, entry 3).

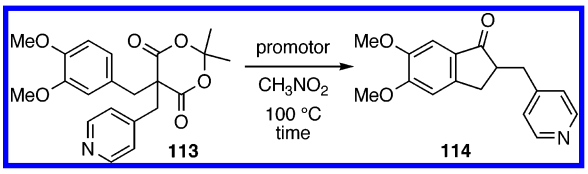
TABLE 5. Donepezil Synthesis



entry	promotor	loading (mol %)	reaction time	yield (%)
1	$Sc(OTf)_2$	15	28 h	NR
2	$Sc(OTf)_3$	170	4 h	N/A
3	TfOH	120	30 min	61

The striking observations made with substrate **111** led to the conclusion that the presence of a basic sp^3-hybridized amine was problematic. In an attempt to circumvent this issue, the synthesis of indanone **114** from Meldrum's acid **113** was explored (Table 6). The sp^2-hybridized nitrogen in **113** should be less prone to interact with the catalyst and reduce its activity. Furthermore, the transformation of indanone **114** into donepezil hydrochloride has been reported.[68] Unfortunately, all attempts to form **114** under catalytic conditions were unsuccessful and starting material was recovered (Table 6, entries 1, 2, 6, and 8). Triflic acid cleanly promoted the formation of indanone **114** in 77% yield (Table 6, entry 3), but TFA or a 5:1 mixture of TFA/TfOH failed. The decomposition of the starting material (Table 6, entry 7) was observed with excess $BF_3{\cdot}OEt_2$. The volatile TMSOTf, when used in slight excess, induced the Friedel–Crafts acylation and indanone **114** was isolated in a 62% yield (Table 6, entry 9).

TABLE 6. Acylation of Pyridine-Containing Substrate 113

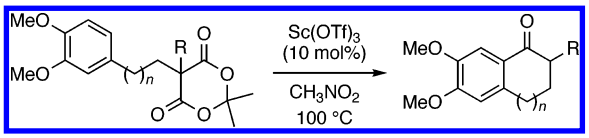


entry	promotor	loading (mol %)	reaction time (h)	yield (%)
1	$Sc(OTf)_3$	10	0.33	NR
2	$Sc(OTf)_3$	40	14	NR
3	TfOH	120	1	77
4	TFA	120	3	NR
5	TFA/TfOH	100/20	44	NR
6	$BF_3{\cdot}OEt_2$	10	19	NR
7	$BF_3{\cdot}OEt_2$	120	14	N/A
8	TMSOTf	20	19	NR
9	TMSOTf	120	1.5	62

In light of these results, it was concluded that nitrile and nitro groups are compatible with the catalytic protocol, while sp^2- and sp^3-hybridized nitrogen-containing functionalities required excess TfOH or Lewis acid to proceed.

1-Tetralone and 1-Benzosuberone Synthesis: Rate of Cyclization as a Function of Ring Size. The use of Meldrum's acid derivatives as the acylating agent in the synthesis of 1-tetralones and 1-benzosuberones was examined. Yield enhancement was significant for the enolizable Meldrum's substrate **115** that furnished tetralone **116** in 82% yield compared to 59% yield for its indanone counterpart **2** (Table 7, entry 1 and Table 1, entry 14). Quaternized Meldrum's acid **117** provided 6,7-dimethoxy-1-tetralone (**118**) in 82% yields (Table 7, entry 2). Moreover, 1-benzosuberones were efficiently formed for both types of Meldrum's acid precursors (Table 7, entries 3 and 4).

TABLE 7. Synthesis of 1-Tetralones and 1-Benzosuberones



entry	substrate	reaction time (min)	product	yield (%)
1	**115**, R = H; $n = 1$	45	**116**, R = H; $n = 1$	82
2	**117**, R = Me; $n = 1$	15	**118**, R = Me; $n = 1$	82
3	**119**, R = H; $n = 2$	45	**120**, R = H; $n = 2$	78
4	**121**, R = Me; $n = 2$	15	**122**, R = Me; $n = 2$	81

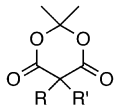
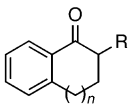
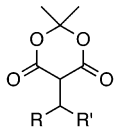
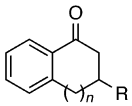
In the Friedel–Crafts acylation, it is well established that 1-tetralones are readily formed in preference to the analogous 1-indanones and 1-benzosuberones.[69] Milder reaction conditions are usually required and higher yields typically obtained. It is widely accepted that the tendency

(66) Deactivation of $La(OTf)_3$ by DABCO, see: Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McCague, R. *J. Org. Chem.* **1998**, *63*, 7183–7189.

(67) Fukuzawa, S.; Komuro, Y.; Nakano, N.; Obara, S. *Tetrahedron Lett.* **2003**, *44*, 3671–3674.

(68) Vidyadhar, J. S.; Venkatraman, N. A.; Pandurang, S. R. U.S. Patent 6,649,765.

TABLE 8. Competition Experiments

entry	substrate	product	yield[a] (%)
1	 **123**, R = CH_2Ph; R' = $(CH_2)_2Ph$	 **124**, n = 1; R = CH_2Ph	75[b]
2	**125**, R = CH_2Ph; R' = $(CH_2)_3Ph$	**126**, n = 2; R = CH_2Ph	77[b]
3	**127**, R = $(CH_2)_2Ph$; R' = $(CH_2)_3Ph$	**128**, n = 1; R = $(CH_2)_3Ph$	76[b]
4	 **129**, R = Ph; R' = CH_2Ph	 **130**, n = 1; R = Ph	51[c]
5	**131**, R = Ph; R' = $(CH_2)_2Ph$	**132**, n = 2; R = Ph	42[c]
6	**133**, R = CH_2Ph; R' = $(CH_2)_2Ph$	**134**, n = 1; R = $(CH_2)_2Ph$	59[c]

[a] The acylation was carried out with $Sc(OTf)_3$ (10 mol %) in CH_3NO_2 at 100 °C. [b] Reaction time is 45 min. [c] The substrate was added by syringe pump, over approximately 8 h, followed by an additional ~1 h at reflux.

toward formation of various ring sizes favors 6 > 5 > 7.[1g] Contrary to the expected order of reactivity, 1-benzosuberone formation was facile for the enolizable Meldrum's substrate, (Table 4, entries 3) when compared to the analogous 1-indanone (Table 1, entry 14). To probe the effect of tether length on the relative rate of cyclization, substrates that could give mixtures of products of various ring size were synthesized. The study was realized in the enolizable and non-enolizable Meldrum's acid substrates series with $Sc(OTf)_3$ (10 mol %) in nitromethane at 100 °C. For each of the six models presented in Table 8, crude ^1H NMR and GC-MS analysis showed the exclusive formation of a single benzocyclic ketone. Quaternized Meldrum's acids were efficiently acylated (Table 8, entries 1−3) and 1-tetralones preferentially formed over 1-benzosuberones and 1-indanones.

(69) (a) v. Braun, J.; Manz, G. *Justus Liebigs Ann. Chem.* **1929**, *468*, 258−277. (b) Leuchs, H. *Chem. Ber. Recl.* **1928**, *61*, 144−146.

This set of experiments also confirmed that 1-benzosuberones are generated preferentially over 1-indanones (Table 8, entry 2). An identical trend was observed for the enolizable Meldrum's acids **129**, **131**, and **133** (Table 8, entries 4−6). Therefore, for the intramolecular Friedel−Crafts acylation with Meldrum's acid derivatives, the ring formation preference is 6 > 7 > 5.

Summary

Exploitation of the exceptional electrophilicity and convenient functionalization of Meldrum's acid provides benzocyclic ketones by catalytic intramolecular Friedel−Crafts acylation. Competition experiments determined that the rate of carbocyclization favors 1-tetralone creation, while benzosuberones form in preference to 1-indanones. The mild conditions of this method are compatible with a very wide range of functional groups that would not survive the conditions of conventional Friedel−Crafts acylation reactions. The presence of sp^2- and sp^3-hybridized nitrogen within the substrate appears to inhibit catalyst activity, so stoichiometric promoters are required in these cases.

The operational simplicity and ready availability of all precursors should make this methodology a useful tool for the assembly of substituted 1-indanones, tetralones, and benzosuberones. Mechanistic studies investigating the distinct reactivity of the enolizable versus the quaternized Meldrum's acid substrates are ongoing and will be disclosed in due course.

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Supporting Information Available: Detailed experimental procedures, full characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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