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# A New Mild Method for the C-Acylation of Ketone Enolates. A Convenient Synthesis of β-Keto-Esters, -Thionoesters, and -Thioesters

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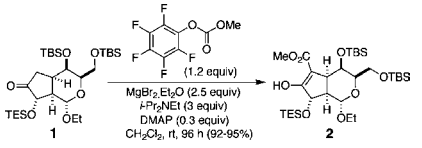
## ABSTRACT




**A new method for ketone enolate C-acylation is described which utilizes alkyl pentafluorophenylcarbonates, thiocarbonates, and thionocarbonates as the reactive acylating agents, and $MgBr_2 \cdot Et_2O$, DMAP, and *i*-$Pr_2NEt$ as the reagents for enolization. A wide range of ketones have been observed to undergo clean C-acylation via this protocol.**

A frequently called-upon reaction in modern-day organic synthesis is the C-acylation of a ketone enolate to obtain the corresponding β-keto ester which, despite the variety of methods that exist for effecting this transformation,[1−4] can sometimes present difficulties in certain situations. One case in point can be found in our recent synthetic route to the antitumor natural product (−)-echinosporin,[5] where there was a requirement to convert ketone **1** into the β-keto ester enol **2**, in high yield, to satisfactorily progress the synthesis. A careful application of all pre-existing ketone enolate C-acylation methods to **1** produced unsatisfactory outcomes, with respect to either reaction yield or the formation of undesired byproducts.

Our first success in this direction came when LiHMDS was used to enolize **1** in THF at −78 °C, and methyl cyano-formate **6** (Mander's reagent)[4] was employed for methoxycarbonylation. These conditions afforded the desired β-keto ester enol **2** in 46% yield (Table 1, entry 2), alongside a multitude of other undesired byproducts. Presumably the latter arose from the starting ketone and the initially formed products, both reacting with the cyanide ion that was being liberated as the reaction progressed, an outcome that has previously been documented[6] for certain ketones when enolate C-acylation is attempted with the Mander reagent and base.

Given the poor outcome of this process with **1**, several alternate C-alkoxycarbonylating agents were evaluated,

(1) For a previous report on the use of LiTMP and an alkyl chloroformate for the C-acylation of ketones, see: Olofson, R. A.; Cuomo, J.; Bauman, B. A. *J. Org. Chem.* **1978**, *43*, 2073. This paper also records that less hindered amide bases such as LDA liberate amines that can sometimes compete more favorably than the enolate itself for the chloroformate.

(2) For examples of the use of acid chlorides to C-acylate Li-enolates, see: Wiles, C.; Watts, P.; Haswell, S.; Pombo-Villar, E. *Tetrahedron Lett.* **2002**, *43*, 2945.

(3) For examples of the use of acyl imidazolides to C-acylate (or O-acylate) ketone enolates, see: Trost, B. M.; Xu, J. *J. Org. Chem.* **2007**, *72*, 9372. This paper also reports that the addition of $BF_3 \cdot Et_2O$ to such reactions reverses the selectivity in favor of the exclusive formation of enol carbonates in high yield.

(4) For examples of the use of Mander's reagent [MeOC(O)CN] for enolate C-acylation, see: (a) Mander, L.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425. (b) Hutt, O. E.; Mander, L. N. *J. Org. Chem.*. **2007**, *72*, 10130. (c) For a recent example of the use of LDA and MeOC(O)CN in THF/DMPU for a ketone kinetic enolization and C-acylation, see: Henderson, J. A.; Phillips, A. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 8499. (d) For the use of LDA/THF/HMPA and Mander's reagent for ketone C-acylation, see: Beshore, D. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **2007**, *129*, 4148. (e) For another successful use of LDA/Mander's reagent/THF at −78 °C, see: Clive, D. L. J.; Sannigrahi, M.; Hisaindee, S. *J. Org. Chem.* **2001**, *66*, 954. (f) For the concurrent occurrence of competing O-acylation during an attempted enolate C-acylation with MeOC(O)CN, see: Mander, L. N.; Thomson, R. *J. Org. Chem.* **2005**, *70*, 1651.

(5) Flasz, J. T.; Hale, K. J. *Org. Lett.* **2012**, *14*, 3024.

(6) For the recent documentation of cyanohydrin byproducts being formed as major reaction products during a KHMDS-mediated ketone enolization and C-acylation with MeOC(O)CN, see: Kazimierski, A.; Kałuża, Z.; Chmielewski, M. *ARKIVOC* **2004**, *3*, 213.

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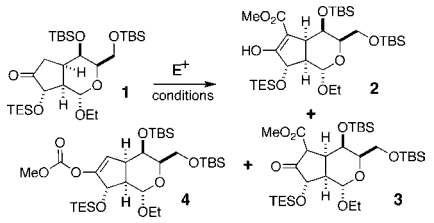
**Table 1.** Attempted Kinetic Enolization and C-Acylation of **1**



| entry | conditions | $E^+$ | product |
|---|---|---|---|
| 1 | KHMDS, THF, -78 °C, 2 h | 5 | **4** (42%) |
| 2 | LiHMDS, THF, -78 °C | 6 | **2** (46%) plus many by-products |
| 3 | KHMDS, THF, -78 °C to rt, 3 h | 7 | Recovered **1** |
| 4 | KHMDS, THF, -78 °C, 1 h | 8 | **3** (15%) |
| 5 | $MgBr_2{\cdot}Et_2O$, *i*-$Pr_2NEt$ $CH_2Cl_2$, rt, 10 min then add DMAP stir, 1 h 10 min | 8 | **2** (26%) plus desired β–keto ester **3** (42%) (68% overall) |
| 6 | $MgBr_2{\cdot}Et_2O$, *i*-$Pr_2NEt$ DMAP, $CH_2Cl_2$, rt, 96 h | 8 | **2** (92%) exclusively |

including methoxycarbonyl imidazolide **7** and methyl pentafluorophenyl carbonate **8**. Both were deemed suitable because of their ability to liberate a non-nucleophilic counteranion following enolate C-acylation. KHMDS was the base initially selected for study, and with **7** as the electrophile, no apparent reaction took place (Table 1, entry 3). However, when **8** was deployed, the desired product **3** was formed cleanly in low yield (15%) (Table 1, entry 4). The success of this reaction prompted us to seek other alternative methods for kinetically enolizing **1** and subsequently trapping with **8**.

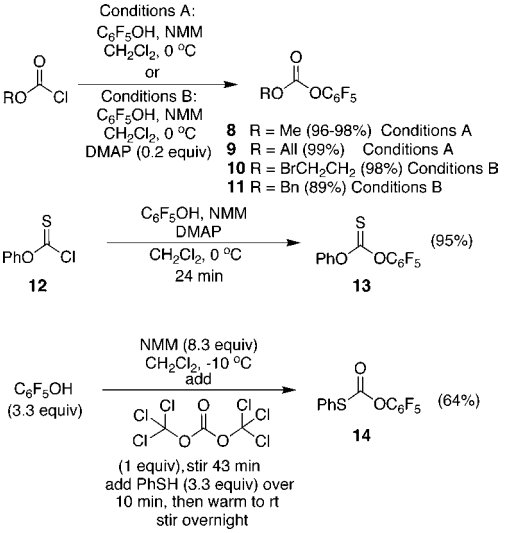
In this connection, we became interested in several recent reports from the Coltart laboratory,[7] where $MgBr_2{\cdot}OEt_2$ and Hunig's base were used to generate bromomagnesium enolates from methyl ketones and thioesters. These were then employed for Claisen condensations with alkyl pentafluorophenyl esters and *N*-acylbenzotriazoles to obtain 1,3-diketones and *β*-keto-thioesters in good yield. Notable for their absence from these studies, however, were electrophiles such as alkyl pentafluorophenyl carbonates, thiophenyl pentafluorophenyl carbonates, and aryl pentafluorophenyl thionocarbonates, which did not auger well for the problem we had at hand.

This observation notwithstanding, when we subjected **1** to Coltart's "soft" enolization conditions in $CH_2Cl_2$, at rt, in the presence of **8**, we observed that no reaction was occurring after 10 min; we therefore added DMAP, and after stirring for a further 70 min, a separable mixture of **2** and **3** was cleanly produced in 68% overall yield (Table 1, entry 5). Despite the greatly improved outcome, this was a level of performance that we wished to further enhance, and it led us to examine whether a prolonged reaction time might be beneficial. Extending the reaction time to 96 h now produced the desired enol **2** exclusively in 92–95% yield.[5]

The great success of these refined kinetic enolization/C-methoxycarbonylation conditions was striking, for they left the adjacent α-keto stereocenter chemically undisturbed, and they produced an excellent yield of the desired product **2** from a system that had consistently failed to give good results when it was submitted to all pre-existing enolate C-acylation methods. Recognizing the great potential of this new transformation, we tested its synthetic applicability on other substrates and report our findings.

Our early effort focused upon devising a good way of preparing the various pentafluorophenyl alkyl carbonates, thionocarbonates, and phenylthiocarbonates that would be needed for our study (Scheme 1). For methyl pentafluorophenyl carbonate **8**, allyl pentafluorophenyl carbonate **9**, and bromoethyl pentafluorophenyl carbonate **10**, these were all readily prepared by treating the corresponding commercially available chloroformates with pentafluorophenol (1 equiv) and *N*-methylmorpholine (NMM) in $CH_2Cl_2$ at 0 °C, and in the case of **10** and benzyl pentafluorophenylcarbonate **11**, a catalytic amount of DMAP was also added. Via this approach, high yields of the desired electrophiles were obtained (89–98%). For the preparation of phenyl pentafluorophenyl thionocarbonate **13**, *O*-phenyl chlorothionoformate **12** served as the active electrophile for the pentafluorophenol, and DMAP was once again added. For thiophenyl pentafluorophenyl carbonate **14**, triphosgene was the initial electrophile, it being sequentially reacted with pentafluorophenol and thiophenol in $CH_2Cl_2$, in the presence of NMM. In the case of **13**, it was obtained in 95% yield as a crystalline solid, while **14** was isolated in 64% yield as an oil. All of these compounds

**Scheme 1.** Methods Used to Prepare **8**–**11**, **13**, and **14**




(7) (a) Lim, D.; Fang, F.; Zhou, G.; Coltart, D. *Org. Lett.* **2007**, *9*, 4139. (b) Zhou, G.; Lim, D.; Coltart, D. M. *Synthesis* **2009**, 56.

showed high shelf stability, with **8**–**11** lasting perfectly well for more than a year at rt without special precautions to guard against decomposition. The S-containing carbonates **13** and **14** were also stable at rt, but *they did decompose after prolonged storage in light*.

We have screened a wide range of ketone substrates in this C-acylation with **8** (1.0–1.4 equiv) (Table 2). Although a substantial number of these reactions were successfully performed at rt in $CH_2Cl_2$ with $MgBr_2 \cdot Et_2O$ (2.5 equiv), *i*-$Pr_2NEt$ (3 equiv), and DMAP (0.2 equiv) over 27–65 h (entries 1, 2, 5, and 12), in some instances, it was more advantageous to heat the reactions at reflux to shorten the overall reaction time and boost the product yield. In other cases, it was beneficial to increase the overall quantities of reagent employed at rt. Generally yields were good whichever protocol was selected.

The rt process could be conducted on methyl ketone **15** without any difficulty (entry 1). Here, a 2.15:1 keto–enol mixture was obtained in 66% yield, while, for 2-acetylthiophene **20**, a 23:1 keto–enol mixture of C-acylated products **21** and **22** resulted in a 89% yield. In both systems, the reactions proceeded cleanly. Propiophenone **18** also reacted reasonably well, affording β-keto ester **19** in 61% yield.

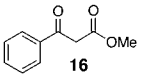
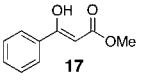
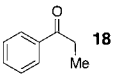
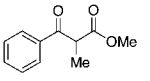
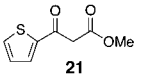
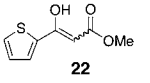
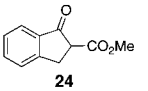
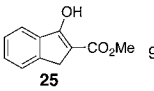
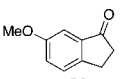
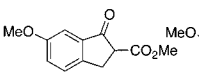
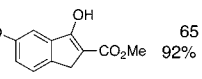
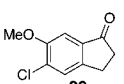
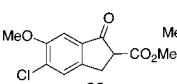
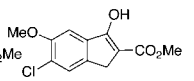
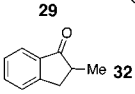
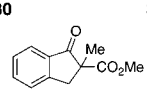
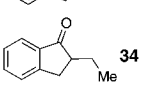
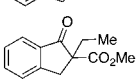
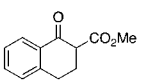
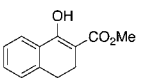
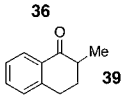
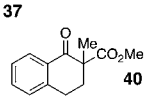
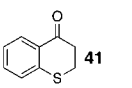
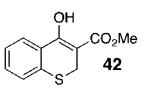
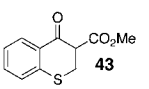
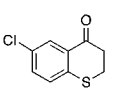
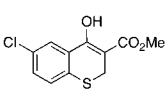
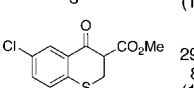
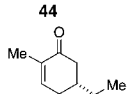
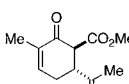
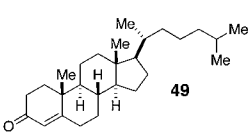
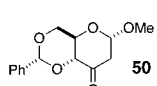
1-Indanones were particularly good substrates for this enolate C-acylation, with ketones **26**, **29**, and **32** all giving rise to high yields of product, and 2-alkyl-substituted 1-indanones working especially well. The latter behavior contrasted sharply with 2-methyl-1-tetralone **39** (entry 10), where the α-substituent proved detrimental, due the development of allylic strain in the enolate. Nonetheless, **39** was still a viable substrate, delivering a workable 43–53% yield of **40**.

We also investigated the feasibility of using α-unsubstituted enones as substrates and carvone **47** worked very well in this regard (Table 2, entry 13, 68–94% yield of **48**). Yet, we must emphasize that not all complex enone substrates have worked as well as carvone. For example, (+)-4-cholesten-3-one **49** produced a highly complex mixture of products when enolate C-acylation was attempted with **8** at rt (Table 2, entry 14). The monosaccharide-derived ketone **50**[8] also underwent serious decomposition with **8** at rt (Table 2, entry 15).

Another key reaction parameter that we have carefully investigated is how steric crowding around the α- and β-carbons of the ketone affects the performance of these bromomagnesium enolate acylation reactions with **8** (Scheme 2). In the case of (−)-menthone, the stereochemical integrity of the α-isopropyl stereocenter was also compromised to some degree. Nonetheless, very useful and workable results were still obtained with cyclopentanone systems, as evidenced by the formation of **57** in 67% yield from (−)-α-thujone **56**. Here the inclusion of catalytic DMAP was found to be essential for reaction progression, with its presence bolstering the yield of **57** from 17% to 67% in a greatly reduced reaction time. Notably, this $CO_2Me$ was installed next to a quaternary carbon.

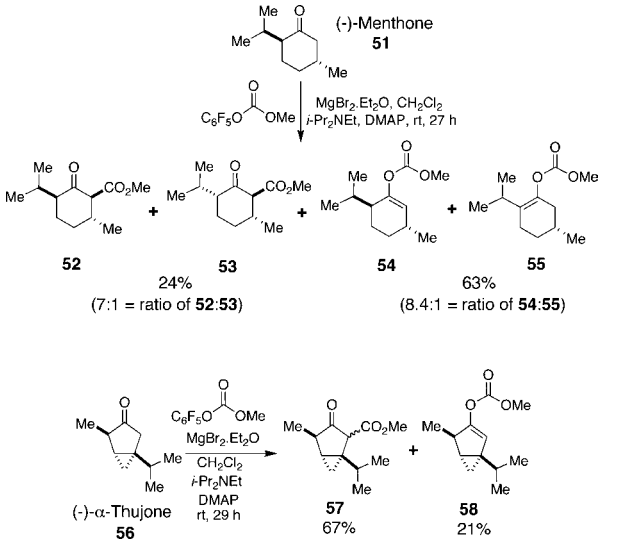
Importantly, 4-oxo-thiochromanones (Table 2, entries 11 and 12), and β-keto ester products with labile alkyl bromides at other positions (Table 3, entry 4), all survived the application of our new enolate C-acylation method. The capacity to efficiently install allyloxycarbonyl and benzyloxycarbonyl functionality α- to a ketone is a particularly useful and notable aspect of this invention (Table 3, entries 1–3), as is the ability to construct

**Table 2.** Outcomes of the $MgBr_2 \cdot Et_2O$/*i*-$Pr_2NEt$/DMAP Mediated C-Acylations of Various Ketones with **8** in $CH_2Cl_2$

| entry | starting ketone | product(s) | time, temp yield (keto/enol) |
|---|---|---|---|
| 1 |  **15** |  **16**  **17** | 27 h, rt 66% (2.15:1) |
| 2 |  **18** |  **19** | 41 h, rt 61% (97:1) |
| 3 |  **20** |  **21**  **22** | 48 h, Δ 89% (23:1) |
| 4 |  **23** |  **24**  **25** | 68 h, Δ 94% (2.7:1) |
| 5 |  **26** |  **27**  **28** | 65 h, rt 92% (7.9:1) |
| 6 |  **29** |  **30**  **31** | 72 h, Δ 70-84% (3.3:1) |
| 7 |  **32** |  **33** | 24 h, Δ 81-91% |
| 8 |  **34** |  **35** | 43 h, Δ 95% |
| 9 |  **36** |  **37**  **38** | 24 h, Δ 82% (1:1.1) |
| 10 |  **39** |  **40** | 48 h, Δ 43-53% |
| 11 |  **41** |  **42**  **43** | 83 h, Δ 70-89% (1:2.2) |
| 12 |  **44** |  **45**  **46** | 29 h, rt 88% (1:5.7) |
| 13 |  **47** |  **48** | 48 h, Δ 68% |
| 14 |  **49** | Complex mixture | |
| 15 |  **50** | Decomposition | |

(8) Manaviazar, S.; Frigerio, M.; Bhatia, G. S.; Hummersone, M. G.; Aliev, A. E.; Hale, K. J. *Org. Lett.* **2006**, *8*, 4477.

**Scheme 2.** Some Examples of the $MgBr_2 \cdot Et_2O/i\text{-}Pr_2NEt$/DMAP/**8** Mediated Kinetic C-Acylation of Hindered Ketones




$\beta$-keto-thioesters (Table 3, entry 5) and rarely encountered $\beta$-keto-thionoesters[9] (entry 6) which, because of their thermal instability, must frequently be prepared and purified at rt. The fact that thioesters undergo Pd(0)-catalyzed reduction to aldehydes with $Et_3SiH$ makes this a potentially useful new way of introducing a masked aldehyde grouping into an organic molecule.[10] Thioesters also undergo Pd(0)-mediated Liebeskind–Srogl cross-couplings with boronic acids.[11] Nicolaou et al. have additionally found multiple new synthetic uses for thionoesters in their brevetoxin work.[12] $\beta$-Keto-allyl esters such as **61** are also exceedingly useful substrates for the Stoltz–Trost Pd(0)-catalyzed asymmetric decarboxylative C-allylation reaction.[13]

**Table 3.** $MgBr_2 \cdot Et_2O/i\text{-}Pr_2NEt$/DMAP Mediated Kinetic C-Acylation with **9**, **10**, **11**, **13**, and **14** in $CH_2Cl_2$

| entry | starting ketone | product(s) | electrophile time, temp yield (keto/enol) |
|---|---|---|---|
| 1 | **47** | **59**, **60** | **9** 46 h, rt 85% (13.9:1) |
| 2 | **32** | **61** | **9** 42 h, rt 89% |
| 3 | **26** | **62**, **63** | **11** 96 h, rt 82% (6.78:1) |
| 4 | **32** | **64** | **10** 27 h, rt 79% |
| 5 | **26** | **65**, **66** | **14** 45 h, rt 82% (1:10.9) |
| 6 | **26** | **67** (virtually exclusively), **68** | **13** 98 h, rt 61% |

Although, it is possible that such enolate C-acylation reactions proceed by rearrangement of an initially formed enol carbonate, they might equally well be occurring directly, through chelated transition states involving the bromomagnesium enolate and the protonated alkyl pentafluorophenyl carbonate or an alkoxycarbonyl-pyridinium ion[14] in what, essentially, would be a temporarily tethered intramolecular cyclization.[15] Possibly, all these processes are occurring concurrently to different degrees.

In conclusion, while we cannot claim universality of scope for our new ketone enolate C-acylation method, we do believe that it will prove useful in some situations where long-established enolate C-acylation technology has already faltered, as it did for us with **1**.[5] We thus recommend this convenient new rt C-acylation procedure, as both a method of primary choice and one of final resort.

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**Supporting Information Available.** Full experimental procedures and spectra for all compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(9) Sato, M.; Ban, H.; Uehara, F.; Keneko, C. *Chem. Commun.* **1996**, 775.
(10) $Et_3SiH$/Pd(0)-thioester reduction: Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050.
(11) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260.
(12) (a) Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Veale, C. A.; Furst, G. T. *J. Am. Chem. Soc.* **1987**, *109*, 2504. (b) Nicolaou, K. C.; Satao, M.; Theodorakis, E. A.; Miller, N. D. *J. Chem. Soc., Chem. Commun.* **1995**, 1583.
(13) (a) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924. (b) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180. (c) Franckevicius, V.; Cuthbertson, J. D.; Pickworth, M.; Pugh, D. S.; Taylor, R. J. K. *Org. Lett.* **2011**, *13*, 4264.
(14) (a) For DMAP mechanisms for O-acylation, see: Xu, S.; Held, I.; Kempf, B.; Mayr, H.; Steglich, W.; Zipse, H. *Chem.—Eur. J.* **2005**, *11*, 4751. (b) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(15) Such a chelate could operate in the following way: