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Direct Carbon−Carbon Bond Formation via Chemoselective Soft Enolization of Thioesters: A Remarkably Simple and Versatile Crossed-Claisen Reaction Applied to the Synthesis of LY294002

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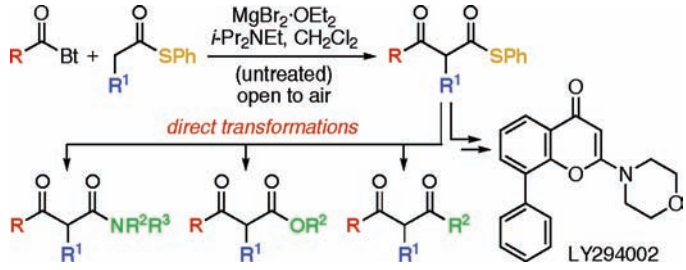
ABSTRACT



Thioesters undergo chemoselective soft enolization and acylation by *N*-acylbenzotriazoles on treatment with $MgBr_2{\cdot}OEt_2$ and *i*-Pr_2NEt to give β-keto thioesters. Prior enolate formation is not required, and the reaction is conducted using untreated CH_2Cl_2 open to the air. The coupled products are stable synthetic equivalents of β-keto acids and can be converted directly into β-keto esters, β-keto amides, and β-diketones under mild conditions. The utility of this carbon−carbon bond-forming method is shown through the synthesis of the PI3-K inhibitor LY294002.

The crossed-Claisen coupling reaction is an essential carbon−carbon bond-forming method.[1] The β-keto ester moiety produced is found in countless natural products, pharmaceuticals, and other compounds in either its native or derivatized form. Indeed, β-keto esters are unusually versatile intermediates, providing access to a very wide array of functionality. In the most general form of the crossed-Claisen reaction, both the nucleophilic precursor and the acylating component possess α-protons. However, in such cases, four products may, in principle, result: two from self- and two from crossed-coupling. Chemoselectivity is controlled using prior enolate formation.[1] While effective, the stepwise procedures required to generate the enolates are time-consuming, particularly if trapping is involved, and require that all manipulations be conducted under anhydrous conditions and, when strong bases are used, at low temperature. Moreover, a large excess of enolate (± acylating agent) is required for high conversion, making these transformations inherently inefficient.[1,2] Given the central role that β-keto esters play in organic synthesis, it is clear that a simplified and more efficient version of this transformation would be beneficial. Herein, we report an efficient and operationally simple direct crossed-Claisen coupling of thioesters and *N*-acylbenzotriazoles via chemoselective soft enolization. The

(1) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed.; Wiley & Sons: Hoboken, 2007; Chapter 16. Benetti, S.; Romagnol, R.; De Risi, C.; Spalluto, G.; Zanirato, V. *Chem. Rev.* **1995**, *95*, 1065–1114.

(2) In a recent modification of the crossed-Claisen reaction, 1:1 mixtures of esters and 2-substituted *N*-acyl-*N*-methylimidazolium chlorides were treated with $TiCl_4$ and Bu_3N, lending some efficiency to the coupling. Unfortunately, the reaction still requires anhydrous conditions and low temperature, and a large excess (3 equiv) of $TiCl_4$ is needed. See: Misake, T.; Nagase, R.; Matsumoto, K.; Tanabe, Y. *J. Am. Chem. Soc.* **2005**, *127*, 2854–2855.

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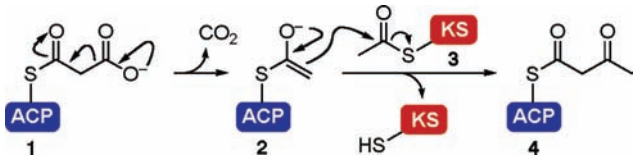
process does not require prior enolate formation and is conducted using untreated, reagent-grade solvent open to the air, thus providing a remarkably simple approach to this important transformation. Moreover, due to their unusual reactivity, the β-keto thioesters produced serve as stable synthetic equivalents of β-keto acids and can be converted directly into a variety of useful compounds under mild conditions, in addition to those commonly obtained from β-keto oxoesters. As a preliminary demonstration of the utility of this method and the strategic advantage imparted by the thioester function, a concise and high-yielding synthesis of LY294002, a potent phosphoinositide 3-kinase (PI3-K) inhibitor, is described.

Soft enolization provides an exceptionally mild and operationally simple approach to direct carbon−carbon bond formation.[3,4] We anticipated that this mode of enolization could provide the basis of a solution to the long-standing problems associated with the crossed-Claisen coupling, provided the nucleophilic precursor could be chemoselectively enolized in the presence of the acylating agent. To achieve this, we turned to the use of simple thioesters as the enolate precursors.[4a,b] Our inspiration for this stems from their pervasiveness in related biological processes. Nature's use of thioesters in forming carbon−carbon bonds is likely due in large part to their enhanced acidity,[5] which ensures appreciable deprotonation by the weak bases found in biological systems. Interestingly, in Nature's version of the crossed-Claisen condensation, such as in fatty acid synthesis (Scheme 1), thioesters serve as both the enolate precursors

Scheme 1. Fatty Acid Biosynthesis (ACP = Acyl-Carrier Protein; KS = β-Ketoacyl-ACPSynthase)



and acylating agents.[6] While such reactions produce a single crossed-product, chemoselective enolization is not achieved by selective deprotonation. Instead, the intended thioester enolate is formed via decarboxylation of the corresponding malonic acid half-thioester (MAHT) (**1**). Although effective in a biological context, we sought a more convenient mode of chemoselective enolization that would avoid the additional steps and difficulties associated with the laboratory preparation of MAHTs.[7] Fortunately, as a result of prior work we had conducted,[4] we felt that chemoselective soft enolization of a simple thioester could be achieved while in the presence of an even more reactive acylating agent.

In our previous studies,[4] we found that thioesters and ketones are readily alkylated under soft enolization conditions, whereas oxoesters, acid chlorides, and *N*-acylbenzotriazoles are not. These observations are consistent with the notion that the propensity of the carbonyl species to enolize is not determined by Brønsted acidity alone, but by a balance between α-proton acidity and carbonyl Lewis basicity (Figure 1). Thus, a carbonyl species that is strongly acidic

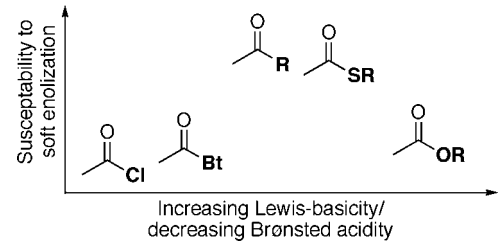


Figure 1. Qualitative relationship between Brønsted acidity, Lewis basicity, and soft enolization.

and, correspondingly, weakly Lewis basic (e.g., acid chloride, *N*-acylbenzotriazole) would be less prone to interaction with the Lewis acid, as required of soft enolization.[4c,d] In contrast, a somewhat less acidic species (e.g., thioester, ketone), being more strongly Lewis basic, would be prone to such interaction and, subsequently, enolization. However, there is a tipping point on this side of the equation too: even though oxoesters are more Lewis basic than thioesters, their relatively low acidity decreases their susceptibility to soft enolization.[4a,b] Thioesters and ketones appear to strike a near ideal balance between Brønsted acidity and Lewis basicity in the context of soft enolization. It is perhaps not surprising then that thioesters are used in biological carbon−carbon bond-forming processes employing soft enolization.

On the basis of the above observations, we anticipated that the use of a thioester as the enolate precursor, in combination with an acid chloride or *N*-acylbenzotriazole as an acyl donor, should enable chemoselective enolization leading to a controlled direct crossed-Claisen coupling. To test this idea, we chose to use *N*-acylbenzotriazoles, which are extremely inexpensive, versatile, and easily managed

(3) For pioneering applications of soft enolization in direct carbon−carbon bond formation, see: Rathke, M. W.; Cowan, P. J. *J. Org. Chem.* **1985**, *50*, 2622–2624. Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2624–2626. Tirpak, R. E.; Olsen, R. S.; Rathke, M. W. *J. Org. Chem.* **1985**, *50*, 4877–4879.

(4) See for example: (a) Yost, J. M.; Zhou, G.; Coltart, D. M *Org. Lett.* **2006**, *8*, 1503–1506. (b) Zhou, G.; Yost, J. M.; Coltart, D. M. *Synthesis* **2007**, 478–482. (c) Lim, D.; Fang, F.; Zhou, G.; Coltart, D. M. *Org. Lett.* **2007**, *9*, 4139–4142. (d) Lim, D.; Zhou, G.; Livanos, A. E.; Fang, F.; Coltart, D. M. *Synthesis* **2008**, 2148–2152.

(5) The pK_a of the thioester α-proton has been reported to be 2 units less than that of the corresponding oxoester. See: Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218–4223.

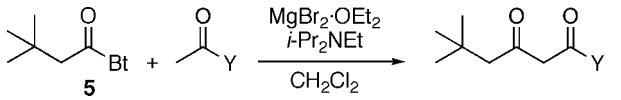
(6) Hill, A. M. *Nat. Prod. Rep.* **2006**, *23*, 256–320. O'Hagan, D. *Nat. Prod. Rep.* **1992**, *9*, 447–479. O'Hagan, D. *The Polyketide Metabolites*; Horwood, E., Ed.; Chichester, UK, 1991.

(7) MAHTs have been used in the development of various carbon−carbon bond forming methods. See for example: Kobuke, Y.; Yoshida, J. I. *Tetrahedron Lett.* **1978**, 367–370. Magdziak, D.; Lalic, G.; Lee, H. M.; Fortner, K. C.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 7284–7285. Lubkoll, J.; Wennemers, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 6841–6844.

(8) For lead refs, see: Katritzky, A. R.; Wang, Z.; Wang, M.; Wilkerson, C. R.; Hall, C. D.; Akhmedov, N. G. *J. Org. Chem.* **2004**, *69*, 6617–6622. (b) Katritzky, A. R.; Suzuki, K.; Wang, Z. *Synlett* **2005**, 1656–1665.

acylating agents.[8,9] Gratifyingly, when *N*-acylbenzotriazole **5** and thioester **6** were combined in CH_2Cl_2 in the presence of $MgBr_2{\cdot}OEt_2$ and Hunig's base (Table 1), the desired

Table 1. Comparison of the Direct Crossed-Claisen Coupling of Various Thioesters and Oxoester **8** with **5**



entry	thio/oxoester	β-keto thio/oxoester	time (h)	yield (%)
1	Y = SPh (**6**)	**7**	4	93
2	Y = OPh (**8**)	**9**	26	44
3	Y = SEt (**10**)	**11**	4	83
4	Y = SBn (**12**)	**13**	4	80

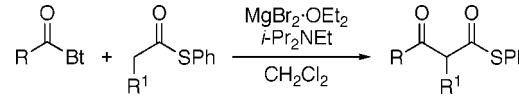
crossed coupling product was obtained in excellent yield (93%). Neither the self-addition products nor the other crossed-Claisen products were detected. To confirm our suspicion regarding the importance of the thioesters in this transformation, oxoester **8** was treated under analogous conditions. In this case, only a relatively low yield (44%) of β-keto oxoester (**9**) formed after an extended period of time, thus confirming the superiority of thioesters in the transformation. The coupling reaction also proceeded with an *S*-ethyl and an *S*-benzyl thioester (**10** and **12**, respectively), albeit with somewhat lower yields.

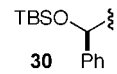
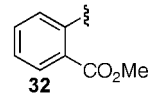
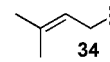
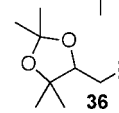
One of the compelling features of conducting carbon−carbon bond formation via soft enolization is the mildness of the reaction conditions required. In avoiding the use of strong bases, not only are low temperature requirements overcome but also there is the need for an inert atmosphere and the use of anhydrous conditions. To test that such conditions would not be deleterious in the present situation, the reaction between **5** and **6** was repeated, but this time open to the air using untreated, reagent grade solvent. We were pleased to find that under these very straightforward conditions there was no change in the outcome of the reaction in comparison to the use of an inert atmosphere and anhydrous conditions.

Having established proof of concept in the direct thioester crossed-Claisen coupling and confirming that it could be conducted without the need for highly controlled conditions, we investigated its scope (Table 2). In general, the transformation proceeded very well with a range of thioesters and *N*-acylbenzotriazoles. The reaction conditions proved to be compatible with a variety of functionality, including ester, acetal, and α,β-unsaturated carbonyl compounds. Notably, it even progressed quite well in the case of a very sterically hindered α-silyloxy substituted *N*-acylbenzotriazole (entry 9).[10]

As demonstrated, the use of thioesters in the direct crossed-Claisen coupling is advantageous in facilitating the reaction

Table 2. Direct Thioester Crossed-Claisen Coupling



entry	R	R^1	β-keto thioester	yield (%)
1	CH_2t-Bu (**5**)	Me (**14**)	**15**	87
2	CH_2t-Bu (**5**)	$CH_2CH_2CH_3$ (**16**)	**17**	85
3	CH_2t-Bu (**5**)	CH_2Ph (**18**)	**19**	88
4	CH_2t-Bu (**5**)	OBn (**20**)	**21**	78
5	Ph (**22**)	Me (**14**)	**23**	91
6	*i*-Pr (**24**)	Me (**14**)	**25**	91
7	*E*-CHCHPh (**26**)	Me (**14**)	**27**	76
8	C_6H_{11} (**28**)	Me (**14**)	**29**	90
9	 **30**	Me (**14**)	**31**	64
10	 **32**	Me (**14**)	**33**	87
11	**32**	 **34**	**35**	92
12	**32**	 **36**	**37**	80

relative to oxoesters. However, in addition, the presence of the thioester moiety in the coupled product enables subsequent direct transformations that are not possible using β-keto oxoesters. Consequently, the β-keto thioesters produced provide a convenient and stable alternative to the use of β-keto acids. For instance, esters were readily formed from β-keto thioester **7** in high yield from alcohols using $AgCO_2CF_3$ as a thiophilic promoter (Scheme 2).[11] The use of allylic alcohols (cf. **39** and **41**) provides straightforward access to Carroll rearrangement substrates (**40** and **42**). Direct amidation[12] was also possible from β-keto thioester **7**, as shown in the preparation of **43** and **45**. An especially useful transformation involving β-keto thioester product **17** is seen in its conversion to β-diketone **46** using the Fukuyama protocol.[13] Overall, this transformation is equivalent to the regioselective acylation of 3-heptanone which, under conventional conditions, would be marginally selective at best. Notably, this is the first report of a direct alkylation of a β-keto thioester.

The usefulness of the present method in preparing β-keto thioesters, along with the strategic advantage presented in their synthetic equivalence to β-keto acids, was demonstrated by a concise total synthesis of LY294002 (**47**), a potent and

(9) We have shown that *O*-Pfp esters are also excellent acylating agents under soft enolization conditions (see refs 4c−d); however, given the relatively high cost associated with their preparation, we have focused on *N*-acylbenzotriazoles for this work.

(10) Control experiments (cf. refs 4c, d) showed that epimerization had not occurred during the formation of **31**.

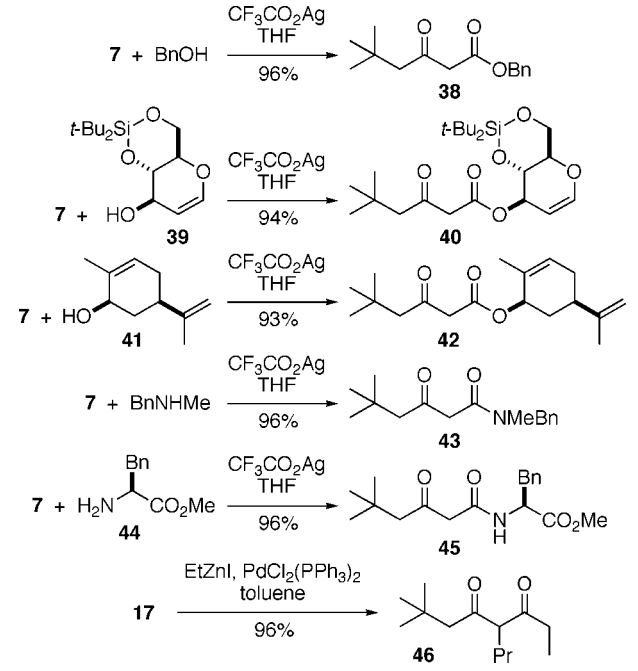
(11) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756–6758.

(12) Ley, S. V.; Smith, S. C.; Woodward, P. R. *Tetrahedron* **1992**, *48*, 1145–1174.

(13) Tokuyama, H.; Yokoshima, S.; Yamashita, T; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189–3192.

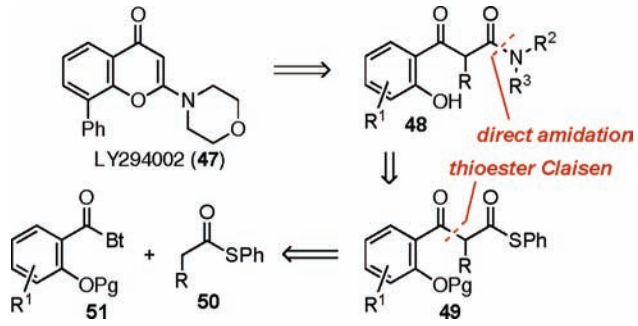
(14) Vlahos, C. J.; Matter, W. F.; Hui, K. Y.; Brown, R. F. *J. Biol. Chem.* **1994**, *269*, 5241–5248.

Scheme 2. Direct Transformations of β-Keto Thioester **7** and **17**



specific inhibitor of PI3-K.[14] PI3-Ks play prominent roles in a variety of diseases including diabetes, cancer, and chronic inflammation and have attracted considerable recent interest as a new class of drug targets.[15] Our plan for the synthesis of **47** is shown in a general sense in Scheme 3.

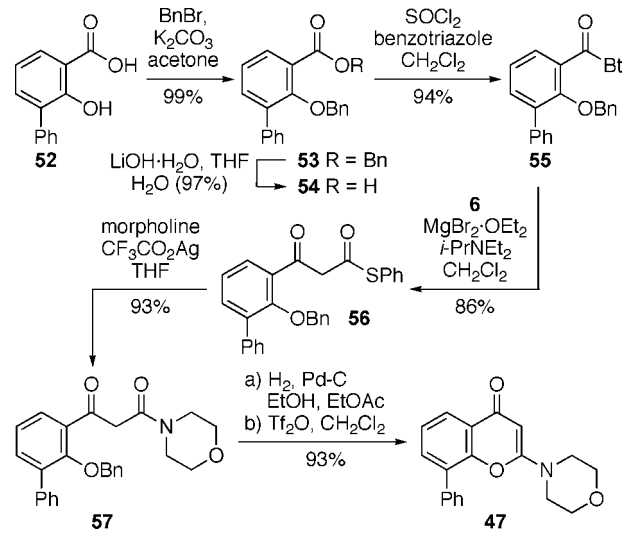
Scheme 3. General Synthetic Strategy for the Synthesis of LY294002 and Structural Analogues



Here, the direct crossed-Claisen coupling of a salicylic acid-derived *N*-acylbenzotriazole and an aliphatic acid-derived thioester is used to merge the two halves of the molecule and is followed by late-stage chemoselective amidation and cyclization. The timing of the amidation reaction (**49** → **48**), along with the established generality of our coupling method, makes this a very simple and flexible approach to structural analogues of LY294002 and related compounds. This should be beneficial for ongoing and future drug development initiatives involving PI3-K.[15]

To test this synthetic strategy, we first prepared *O*-benzyl-protected *N*-acylbenzotriazole **55** from commercially available 3-phenyl salicylic acid (**52**) (Scheme 4). Treatment of

Scheme 4. Synthesis of LY294002



55 and thioester **6** under the conditions developed above smoothly generated β-keto thioester **56**. The thioester function was then leveraged in the direct amidation reaction leading to **57**. Hydrogenolysis followed by treatment with Tf_2O generated the chromone core, thus providing LY294002 with an overall yield of 70%.[16]

In conclusion, we have developed an efficient direct crossed-Claisen reaction between thioesters and *N*-acylbenzotriazoles. The process does not require prior enolate formation and is conducted using untreated, reagent-grade solvent open to the air. In contrast to products obtained via conventional Claisen condensations, the resulting β-keto thioesters serve as stable synthetic equivalents of β-keto acids and readily undergo *direct* conversion to esters, amides, and ketones. The utility of this coupling procedure and the strategic advantage resulting from the presence of the thioester function have been demonstrated through the total synthesis of LY294002.

Acknowledgment. This work was supported, in part, by the ACS Petrolum Research Fund. G. Z. holds a C. R. Hauser Fellowship from the Duke University Department of Chemistry.

Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Ward, S.; Sotsios, Y.; Dowden, J.; Bruce, I.; Finan, P *Chem. Biol.* **2003**, *10*, 207–213. Ward, S. G.; Finan, P. *Curr. Opin. Pharmacol.* **2003**, *3*, 426–434. Walker, E. H.; Pacold, M. E.; Perisic, O.; Stephens, L.; Hawkins, P. T.; Wymann, M. P.; Williams, R. L. *Mol. Cell* **2000**, *6*, 909–919.

(16) In an earlier synthesis, **47** was obtained from **52** in 33% overall yield. See: Abbott, B.; Thompson, P. *Aust. J. Chem.* **2003**, *56*, 1099–1106.