A Practical Synthesis of β-Keto Thioesters by Direct Crossed-Claisen Coupling of Thioesters and *N*-Acylbenzotriazoles

Guoqiang Zhou, Daniel Lim, Fang Fang, Don M. Coltart*

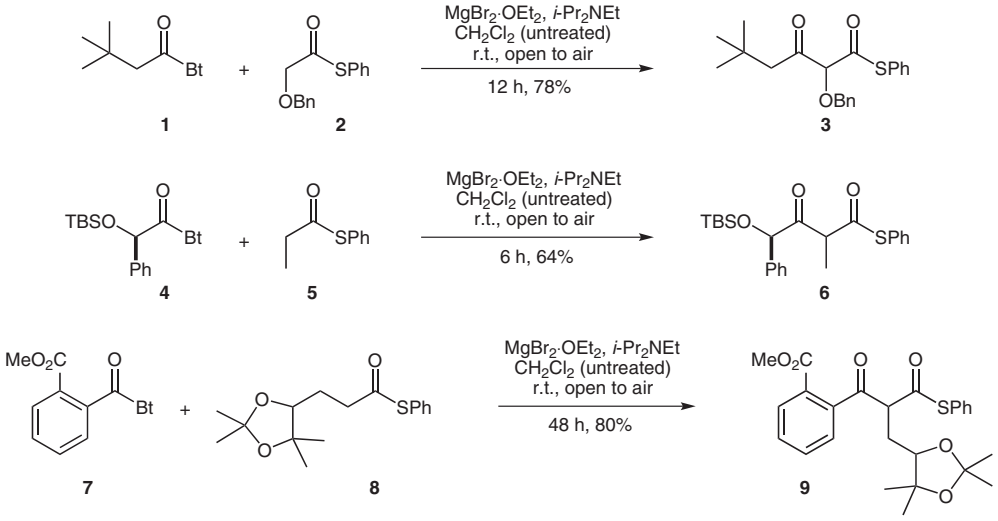
Department of Chemistry, Duke University, Durham, NC 27708, USA
Fax +1(919)6601605; E-mail: don.coltart@duke.edu

Received 13 June 2009

PSP No 169

Abstract: Thioesters undergo chemoselective soft enolization and acylation with *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 dichloromethane open to the air.

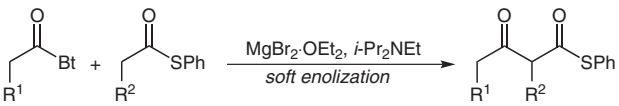
Key words: soft enolization, crossed-Claisen condensation, acylation, thioester, C–C coupling reaction



Scheme 1 Direct thioester crossed-Claisen reaction via soft enolization

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. In situations where both components of the coupling reaction possess α-protons, chemoselectivity is controlled by prior enolate formation.[1] While effective, the step-wise procedures required for enolate formation 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] Herein, we report an efficient and operationally-simple direct crossed-Claisen coupling of thioesters and *N*-acylbenzotriazoles based on chemoselective soft enolization[3] that addresses these limitations (Scheme 1). The 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.

The underlying premise for chemoselectivity in this transformation derives from our earlier observations[4] that, like ketones, thioesters are particularly well suited to soft enolization, whereas *N*-acylbenzotriazoles[5] are relatively less susceptible to this form of enolization. Consequently, combination of a thioester and an *N*-acylbenzotriazole under conditions that promote soft enolization should result in a controlled crossed-Claisen reaction, with the thioester serving as the enolate precursor and the *N*-acylbenzotriazole as the acylating agent (Scheme 2).[4e]



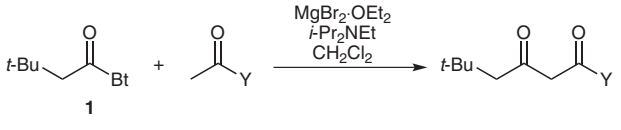
Scheme 2 Direct thioester crossed-Claisen reaction via soft enolization

SYNTHESIS 2009, No. 19, pp 3350–3352
Advanced online publication: 28.08.2009
DOI: 10.1055/s-0029-1216971; Art ID: Z12309SS

This idea was tested by combining *N*-acylbenzotriazole **1** (1.0 equiv) and *S*-phenyl thioester **10** (1.0 equiv) in CH_2Cl_2 (0.25 M) in the presence of $MgBr_2{\cdot}OEt_2$ (3.0 equiv) and Hünig's base (4.0 equiv) (Table 1, entry 1). The desired crossed coupling product was obtained in excellent yield (93%), and neither the self-addition products nor the other crossed-Claisen product was detected. Decreasing the amount of $MgBr_2{\cdot}OEt_2$, Hünig's base, or the concentration of the reaction resulted in a lower yield and longer reaction time. Moreover, increasing the relative amount of the thioester compared to the *N*-acylbenzotriazole gave a slightly lower conversion, along with a small amount of the thioester self-condensation product.

The coupling reaction was tried with a variety of acetate-derived thioesters, as well as with phenyl acetate (Table 1). Of the thioesters examined, **10** was found to perform the best in terms of product yield. As expected, oxoester **22** underwent the transformation much less efficiently, giving only 44% yield of the coupled product after 24 hours.

Table 1 The Direct Crossed-Claisen Coupling of **1** with Various Thioesters and an Oxoester

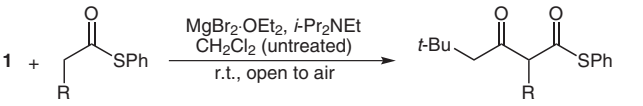


Entry	Y	Product	Time (h)	Yield (%)
1	SPh (**10**)	**11**	4	93
2	SC_6H_4-4-Cl (**12**)	**13**	4	84
3	SC_6H_4-4-CF_3 (**14**)	**15**	4	87
4	SC_6H_4-4-OMe (**16**)	**17**	4	81
5	SEt (**18**)	**19**	4	83
6	SBn (**20**)	**21**	4	80
7	OPh (**22**)	**23**	26	44

One of the compelling features of carbon–carbon bond formation via soft enolization is the mildness of the reaction conditions. In avoiding the use of strong bases, not only are low temperature requirements overcome, but so too is the need for an inert atmosphere and the use of anhydrous conditions. To confirm that such conditions would not be deleterious in the present situation, the reaction between **1** and **10** was repeated, but this time open to the air using untreated, reagent grade solvent. No change in the outcome of the reaction was observed using this extremely simple set of conditions, in comparison to the use of an inert atmosphere and anhydrous conditions.

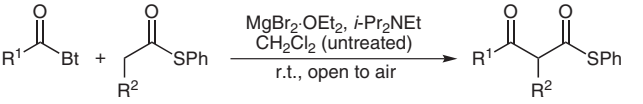
The scope of the reaction with different α-substituted thioesters and **1** was investigated (Table 2). The transformation proved to be compatible with α-alkyl and α-alkoxy thioesters (entries 1 to 4), however, β-alkoxy and β-silyl-

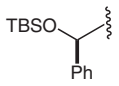
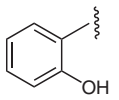
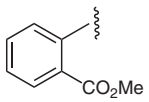
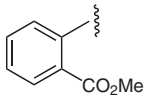
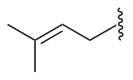
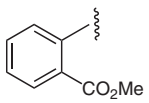
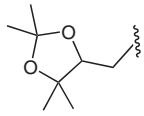
Table 2 The Direct Crossed-Claisen Coupling of **1** with Various Thioesters



Entry	R	Product	Time (h)	Yield (%)
1	Me (**5**)	**24**	6	87
2	Pr (**25**)	**26**	12	85
3	Bn (**27**)	**28**	12	88
4	OBn (**2**)	**3**	12	78
5	CH_2OBn (**29**)	**30**	12	0
6	CH_2OTBS (**31**)	**32**	12	0

Table 3 The Direct Crossed-Claisen Coupling of Thioesters with *N*-Acylbenzotriazoles



Entry	R^1	R^2	Product	Time (h)	Yield (%)
1	Ph (**33**)	Me (**5**)	**34**	48	91
2	*i*-Pr (**35**)	Me (**5**)	**36**	6	91
3	(*E*)-CH=CHPh (**37**)	Me (**5**)	**38**	16	76
4	C_6H_{11} (**39**)	Me (**5**)	**40**	6	90
5	 **4**	Me (**5**)	**6**[a]	6	64
6	 **41**	Me (**5**)	**42**	120	0
7	 **7**	Me (**5**)	**43**	12	87
8	 **7**	 **44**	**45**	24	92
9	 **7**	 **8**	**9**	48	80

[a] Control experiments (cf. refs 4c,d) showed that epimerization did not occur.

oxy thioesters (entries 5 and 6) were not suitable substrates, due to competing β-elimination.

The scope of the reaction was further explored using a variety of *N*-acylbenzotriazoles and different thioesters (Table 3). In general, the transformation proceeded very well with a range of *N*-acylbenzotriazoles, including those possessing ester, acetonide, and α-silyloxy functionality. It was also effective with an α,β-unsaturated *N*-acylbenzotriazole **37**. However, the phenolic species **41** failed to undergo the crossed coupling reaction altogether. Notably, the direct crossed-Claisen reaction proved to be very effective in the formation of sterically hindered systems, as shown in entries 5, 8, and 9.

An additional advantage in using thioesters for the direct crossed Claisen reaction is that the β-keto thioester products act as stable synthetic equivalents of β-keto acids. The thioester products can be directly converted into a variety of useful compounds under mild conditions, in addition to those commonly obtained from β-keto esters. These include β-keto esters, β-keto amides and β-diketones.[4e]

In conclusion, we have developed an efficient direct crossed-Claisen reaction between thioesters and *N*-acylbenzotriazoles. The process is efficient, does not require prior enolate formation, and is conducted using untreated, reagent-grade solvent open to the air.

Unless stated to the contrary, where applicable, the following conditions apply: Reactions were stirred magnetically using Teflon-coated magnetic stirring bars. Stirring bars, syringe needles and glassware were dried in an oven at 120 °C and allowed to cool open to the air prior to use. Commercially available Norm-Ject disposable syringes were used. Commercial grade solvents were used for routine purposes without further purification. Flash column chromatography was performed on silica gel 60 (230–400 mesh).

_S_-Phenyl 2,5,5-Trimethyl-3-oxohexanethioate (24); Typical Procedure

This reaction was conducted using untreated reagent grade CH_2Cl_2, open to the atmosphere. Glassware and stirring bars were dried as described above, but allowed to cool open to the atmosphere. $MgBr_2{\cdot}OEt_2$ (0.387 g, 1.5 mmol) was added to a stirred solution of *S*-phenyl propanethioate (**5**; 0.083 g, 0.5 mmol) in CH_2Cl_2 (2 mL), followed by addition of *N*-acylbenzotriazole **1** (0.109 g, 0.5 mmol) and *i*-Pr_2NEt (0.35 mL, 2.0 mmol). Stirring was continued for 6 h and 10% aq HCl (2 mL) was added. Stirring was continued for 5 min and the mixture was partitioned between EtOAc (30 mL) and H_2O (5 mL). The aqueous phase was extracted with EtOAc (2 × 10 mL) and the combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), and evaporated to give a light-red oil. Flash chromatography over silica gel using 5:95 EtOAc–hexanes gave **24** (0.115 g, 87%) as a pure, light-pink oil comprised of a mixture of the β-keto thioester and tautomeric enol forms in a ratio of 4:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.46 (s, 1 H), 7.52–7.34 (m, 5 H), 3.81 (q, *J* = 7.2 Hz, 1 H), 2.49 (s, 2 H), 2.24 (s, 2 H), 2.00 (s, 3 H), 1.41 (d, *J* = 8.0 Hz, 3 H), 1.04 (s, 9 H), 1.03 (s, 9 H).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 203.8, 196.0, 194.8, 174.1, 135.5, 134.5, 129.8, 129.6, 129.4, 129.3, 127.7, 127.1, 105.3, 62.7, 53.6, 45.6, 33.3, 31.1, 30.3, 29.7, 13.6, 13.1.

MS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{20}O_2S$ + Na: 287.1; found: 287.1.

Acknowledgment

G.Z. holds a C. R. Hauser Fellowship from Duke University Department of Chemistry. This work was supported by Duke University, the ACS (PRF 4650-G1), and NCBC (2008-IDG-1010).

References

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

(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.

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

(4) See, for example: (a) Yost, J. M.; Zhou, G.; Coltart, D. M. *Org. Lett.* **2006**, *8*, 1503. (b) Zhou, G.; Yost, J. M.; Coltart, D. M. *Synthesis* **2007**, 478. (c) Lim, D.; Fang, F.; Zhou, G.; Coltart, D. M. *Org. Lett.* **2007**, *9*, 4139. (d) Lim, D.; Zhou, G.; Livanos, A. E.; Fang, F.; Coltart, D. M. *Synthesis* **2008**, 2148. (e) Zhou, G.; Lim, D.; Coltart, D. M. *Org. Lett.* **2008**, *10*, 3809.

(5) For lead references on *N*-acylbenzotriazoles see, for example: (a) Katritzky, A. R.; Wang, Z.; Wang, M.; Wilkerson, C. R.; Hall, C. D.; Akhmedov, N. G. *J. Org. Chem.* **2004**, *69*, 6617. (b) Katritzky, A. R.; Suzuki, K.; Wang, Z. *Synlett* **2005**, 1656.