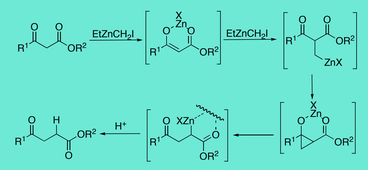
The Tandem Chain Extension-Acylation Reaction

Carley M. Spencer, Amanda M. St. Jean, Jennifer R. Mazzone, Alex M. Jacobine, and Charles K. Zercher
University of New Hampshire, Department of Chemistry
cmm996@unh.edu; Parsons Hall, 23 Academic Way Durham, NH 03824

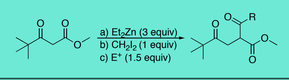
Introduction

Recent research in the Zercher group has focused on the development of a tandem chain extension-acylation reaction. Exposure of a β-keto ester to a zinc-carbenoid followed by addition of an acylating agent results in the formation of an α-acylated γ-keto ester. These acylated products have potential applications toward the synthesis of heterocycles such as furans, pyrans, or thiophenes[1] as well as in the synthesis of spiro-fused acetals.[2]

Zinc-mediated chain extension mechanism[3]

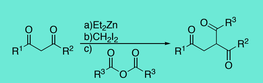


Acylating agents



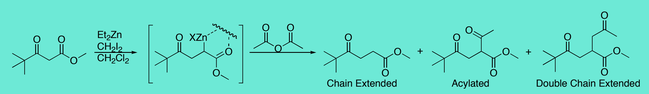
Electrophile	R	% Yield
	Me	77
	Me	0
	Ph	95
	i-Pr	80
	H	-
	Me	48

Scope of β-keto carbonyls



R¹	R²	R³	% Yield
t-Bu	-OMe	Me	63
t-Bu	-OMe	*i*-Pr	80
t-Bu	-OMe	Ph	95
Me		Me	36
Me		Ph	51
Me		Me	36
Me		Ph	73
Ph	-OMe	Me	55
Ph	-OMe	Ph	51
Me		Ph	62
		Ph	80

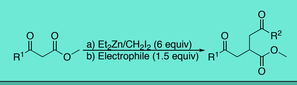
Double chain extension



Et_2Zn (equiv)	CH_2I_2 (equiv)	Anhydride (equiv)	% Chain Extended	% Acylated	% Double Chain Extended
3	3	1	30	24	46
3	1	1.5	17	83	0
4	4	1	28	11	61

[a] Relative abundance using relative integrations from ^1H NMR analysis of the crude reaction mixture

The tandem homologation acylation reaction results in the formation of a new β-keto ester, presenting the opportunity for further homologation. Lowering the equivalents of carbenoid prevents further homologation of the acylated product while adding excess carbenoid allows access to the doubly homologated product.

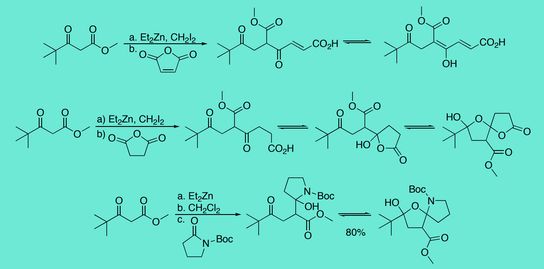


R¹	Electrophile	R²	% Yield
t-Bu		Me	63
t-Bu		*i*-Pr	57
Me		Me	24
t-Bu		Ph	69[a]
Ph		Ph	0
t-Bu		*t*-Bu	0

[a] Double chain extended product was obtained only after resubmitting the intermediate acylated product to zinc-carbenoid in a second pot

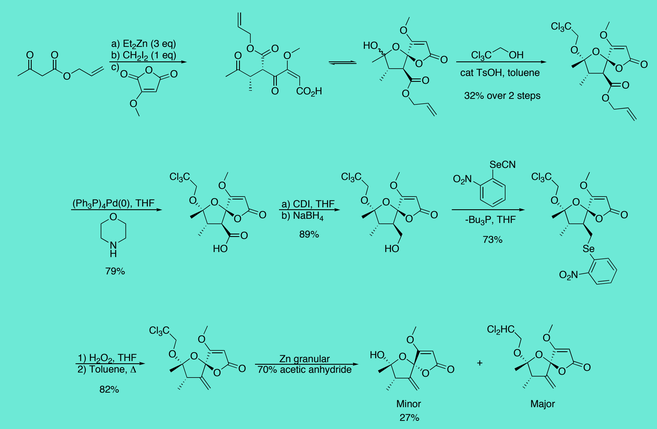
The double chain extension has been shown to provide easy access to 1,5-diketones. The best yields were obtained with sterically unhindered anhydrides. Use of benzotriazole activated pivalic acid as an acylating agent was unsuccessful, most likely due to the steric bulk of the *t*-butyl group.

Cyclic acylating agents

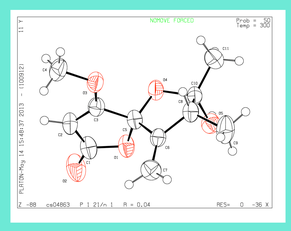


Cyclic acylating agents were used to target spiro-fused ketal systems. Use of maleic anhydride resulted in the isomerization to the trans olefin preventing the product from forming a spiro-fused acetal. Addition of succinnic anhydride resulted in a mixture of isomers with both the open-chain and spiro-fused acetal present by NMR analysis. Use of N-Boc protected pyrolidinone as an acylating agent demonstrated the ability to form oxa-azaspiro compounds.

Papyracillic acid A



Papyracillic acid A is an antibiotic isolated from the ascomycete fungus *Lachnum papyraceum*[4]. The tandem chain-extension acylation reaction in which allyl acetoacetate was exposed to methyl substituted zinc-carbenoid followed by the addition of 3-methoxymaleic anhydride resulted in the formation of 4 new stereocenters and the installation of the spiro-fused ketal core of papyracillic acid. Deallylation and reduction of the allyl ester yielded the corresponding alcohol, which was then converted to an exocyclic double bond through a Grieco reaction.[5] Deprotection of the 2,2,2-trichloroethyl protecting group resulted in the formation of papyracillic acid A with the reduced dichloroethyl compound as a major byproduct.



X-ray crystal sturcture of papyracillic acid A[6]

Conclusions

The tandem chain-extension acylation reaction has been successfully applied to the formation of α-acylated 1,4-dicarbonyls in good yield from a variety of starting 1,3-dicarbonyls. Cyclic and acyclic anhydrides, benzotriazole activated carboxylic acids, and cyclic imides can be used as acylating agents. Addition of excess zinc-carbenoid allows for the formation of 1,5-diketones through a second homologation. The tandem chain-extension acylation reaction has been successfully applied toward the synthesis of the papyracillic acid family of natural products.

References

[1] Bird, C. W.; Cheeseman, G. W. H., *Comprehensive Heterocyclic Chemistry*. Pergamon: Oxford, 1984; Vol. 4
[2] Mazzone, J. R.; Zercher, C. K. *J. Org. Chem.* **2012**, 77 (20), 9171-9178
[3] Eger, W. A.; Zercher, C. K.; Williams, C. M. *J. Org. Chem.* **2010**, 75, 7322-7331
[4] Shan, R.; Stadler, M.; Anke, H.; Sterner, O. *Tetrahedron* **1997**, 53 (17), 6209-6214
[5] Mizuno, M.; Cava, M. P.; Garito, A. F. *J. Org. Chem.* **1976**, 41 (8), 19176
[6] Briggs, J.; Miller, G. P., X-Ray crsytal structure solved for CS04-86_(5S,7R,8S)-7-Hydroxy-4-methoxy-7,8-dimethylene-1,6-dioxaspiro[4.4]non-3-en-2-one. University of New Hampshire: 2013