Tetrahedron Letters 49 (2008) 5983–5985

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Multicomponent reaction design: a one-pot route to substituted di-*O*-acylglyceric acid amides from α-diazoketones

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ARTICLE INFO

Article history:
Received 17 June 2008
Accepted 29 July 2008
Available online 3 August 2008

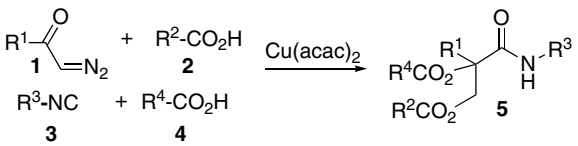
ABSTRACT

A four-component assembly of substituted di-*O*-acylglyceric acid amides has been developed from α-diazoketones. The process involves copper-catalyzed reaction of the α-diazoketone with a carboxylic acid, and subsequent Passerini condensation of the in situ formed α-acyloxyketone.

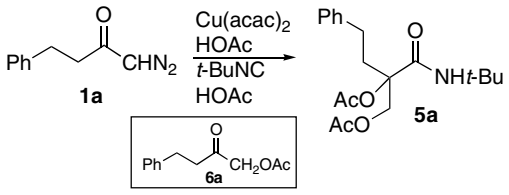
Multicomponent reactions (MCRs) have attracted the attention and interest of synthetic chemists as efficient processes for the assembly of densely functionalized structures. MCRs are of special interest in making compounds that exhibit pharmacological activity.[1] As part of our laboratory's effort to expand the repertoire of useful MCRs, we have investigated the utility of functionalized carbonyl compounds such as acyl cyanides[2] and acyltetrazoles[3] in isonitrile-based multicomponent condensations, whose scope has traditionally been limited to simple aldehydes and ketones.[4] Here, we report a versatile, 4-component condensation of readily available α-diazoketones with (two) carboxylic acids and isonitriles to afford a new family of structurally diverse, substituted di-*O*-acylglyceramides **5** (Scheme 1).

By suitable manipulation of the glyceramide framework in **5**, the method can be used to create new families of synthetic amphiphilic compounds having potential applications as surfactant-active compounds and as carriers for drug encapsulation and delivery.

Simple α-diazoketones proved refractory to the standard conditions of the Passerini or Ugi condensations, even when heated to 60–70 °C. However, α-diazoketones and sulfonic acids spontaneously formed β-ketosulfonates, a family of reactive carbonyls that were recently utilized in a new Ugi-based approach to substituted 2-oxazolines.[5]



Scheme 1.



Scheme 2.

We therefore investigated two-stage, one-pot MCRs of the representative diazoketone **1a** (Scheme 2) triggered by an initial metal-catalyzed insertion into a typical carboxylic acid (e.g., HOAc),[6,7] followed by an in situ Passerini condensation as shown. With $Rh_2(OAc)_4$ as catalyst, complex product mixtures were formed from which only minor quantities of the initial insertion product 1-acetoxy-4-phenyl-2-butanone **6a** could be isolated. However, using $Cu(acac)_2$ (10 mol %),[7] the desired di-*O*-acylglyceramide **5a** was obtained in 68% yield, along with **6a** (26%).

Optimization of this 4-component reaction led to several interesting findings. To begin with, Shinada et al. used relatively large quantities of $Cu(acac)_2$ (10 mol %) for the initial diazoketone insertion reaction, raising the concern that copper complexation of the isonitrile component might cause a sequestering effect that would interfere with the subsequent Passerini condensation leading to **5**. To investigate this question, a pure sample of 1-acetoxy-4-phenyl-2-butanone **6a** was subjected to the Passerini reaction leading to **5a** with and without $Cu(acac)_2$ (5 mol %), and the progress of the condensation was monitored by following disappearance of the ketoacetate, as shown in Figure 1.

As the data in Figure 1 illustrate, $Cu(acac)_2$ exerted a mild rate-retarding effect on the formation of **5a**. A similar effect was also noted in Passerini reactions of the parent ketone, 4-phenyl-2-butanone, which suggested that complexation by $Cu(acac)_2$ depleted the reaction medium of the key of the isonitrile reactant. Besides explaining the modest yield of **5a**, isonitrile sequestration by

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doi:10.1016/j.tetlet.2008.07.167

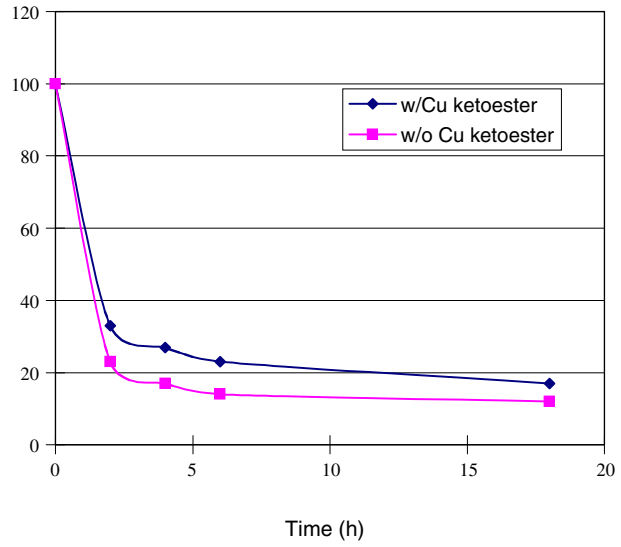

Figure 1.

copper also accounted for the recovery of significant quantities of unreacted ketoacetate **6a**.

One successful solution to the problem involved using excess isonitrile. However, to optimize the synthetic efficiency of the process we investigated whether lower catalyst loads might also improve the yields of **5**. Dropwise addition of diazoketone **1a** (1.3 equiv) into a toluene solution (60 °C, 30 min) of acetic acid and 1.0 mol % of $Cu(acac)_2$ followed by in situ Passerini condensation afforded **5a** in 94% yield. Upon further experimentation, we observed that the diazoketone insertion reaction could be achieved equally well in most cases *without any metal catalyst*, although the somewhat higher temperatures required (100–110 °C) led us to favor the use of 1 mol % $Cu(acac)_2$ in most circumstances.

Table 1 summarizes the scope and versatility of the new four-component synthesis of di-*O*-acylglyceric acid diamides depicted in Scheme 1, which has been successfully implemented as a one-pot process.

The initial insertion reactions were monitored by N_2 evolution and usually required heating for 30–60 min at 60–90 °C. In reactions using diazoketones **1a**–**c**, 1.3 equiv of diazoketone was used, whereas insertions using diazoacetone **1d** were optimally achieved using 1.8 equiv of diazoketone. The scope of the new four-component condensation appears to be limited to aliphatic diazoketones. In the case of benzoyldiazomethane, the initial insertion was successful, but the α-acyloxyketone failed to undergo the subsequent Passerini reaction.

The product glyceramides **5** were formed as racemic mixtures. With respect to controlling the new stereogenic center formed in the second step of the MCR, we were intrigued by a recent paper by Andreana et al., reporting that certain α-substituted aldehydes capable of bidentate binding underwent enantioselective Passerini reactions using an indan (pybox) Cu(II) Lewis acid complex.[8] Using the synthesis of 5 h as a test case, diazoketone **1d** was reacted with isobutyric acid in the absence of $Cu(acac)_2$ to form the corresponding acyloxypropanone. The subsequent Passerini reaction was conducted in the presence of indan (pybox) Cu(II) catalyst (20 mol %) following the protocol of Andreana et al. and produced 5 h with no measurable enantiomeric excess.

The new MCR represents a more selective and efficient alternative to the stepwise introduction of carboxylic ester groups into the *vic*-diol backbone of glyceramides, since it avoids the potential for ester interchange by competing *O*,*O*-acyl transfer side reactions. As one illustration of its utility, we describe the synthesis of a 'facially amphiphilic'[9] diester **5i** containing one lipophilic and one hydrophilic side chain, each derived from a carboxylic acid.

Representative experimental procedure—synthesis of diester **5b—A** mixture of acetic acid (57 μL, 1.0 mmol) and $Cu(acac)_2$ (2.6 mg, 0.01 mmol, 1 mol %) in toluene (2 mL) in a 10 mL round bottomed flask was heated to 60 °C for 10 min under nitrogen. To it was added dropwise a solution of diazoketone **1a** (226 mg, 1.3 mmol, 1.3 equiv) in toluene (2 mL). Once gas evolution was judged complete, the reaction mixture was stirred for an additional 5 min, then cooled and concentrated in vacuo. The oily residue was blanketed in nitrogen, then treated with *iso*-butyric acid (140 L, 1.5 mmol, 1.5 equiv) and *t*-BuNC (170 L, 1.5 mmol, 1.5 equiv). The resulting reaction mixture was stirred at rt under N_2 for 20 h. The product was purified by flash column chromatography (1:1 EtOAc/hexanes, R_f = 0.3) to afford **5b** (338 mg, 90%) as a pale yellow oil.[10]

Table 1
$Cu(acac)_2$-catalyzed 4-Component Condensations of R^1COCHN_2, R^2CO_2H, R^3NC, and R^4CO_2H leading to **5**

1 R^1 =	**2** R^2 =	**3** R^3 =	**4** R^4 =	Product (yield) (%)
$Ph(CH_2)_2$**1a**	CH_3	*t*-Bu	CH_3	**5a** (94)
1a	CH_3	*t*-Bu	$(CH_3)_2CH$	**5b** (90)
1a	Ph	EtO_2CCH_2	C_7H_{15}	**5c** (72)
C_7H_{15}**1b**	$(CH_3)_2CH$	*t*-Bu	$CbzNHCH_2$	**5d** (70)
1b	Ph	*cyclo*-C_6H_{11}	CH_3	**5e** (80)
cyclo-C_6H_{11}**1c**	C_7H_{15}	*n*-Bu	CH_3	**5f** (70)
1c	$NCCH_2$	EtO_2CCH_2	Ph	**5g** (76)
CH_3**1d**	$(CH_3)_2CH$	*n*-Bu	$CbzNHCH_2$	**5h** (71)
1d	$H(CH_2O\text{-}CH_2)_3$	*t*-Bu	C_7H_{15}	**5i** (58)

Acknowledgments

Financial support from Johnson & Johnson's Focused Giving Grant Program is gratefully acknowledged. One of us (LF) wishes to thank the Sien Moo Tsang endowment for a graduate fellowship. Support of the Cornell NMR Facility has been provided by NSF and NIH.

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10. *Spectroscopic data for representative new compounds*: for **5b**: ^{1}H NMR (300 MHz, $CDCl_3$)™ 7.12–7.28 (m, 5H), 6.39 (s, 1H), 4.90 (d, 1H, *J* = 11.5 Hz), 4.42 (d, 1H, *J* = 11.5 Hz), 2.46–2.61 (m, 4H), 2.28 (m, 1H), 2.02 (s, 3H), 1.41 (s, 9 H), 1.20 (dd, 6H, *J* = 7.0, 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$)™ 174.53, 170.15, 168.63, 140.86, 128.71, 128.67, 126.40, 85.74, 64.98, 51.64, 35.05, 33.35, 29.72, 28.93, 20.86, 19.35, 19.21; IR (neat) 3438(s), 2970(s), 1745(s), 1691(s); CIMS (methane) *m/z*: 378.3 (M+H), 308.2, 209.2.
For **5c**: ^{1}H NMR ($CDCl_3$)™ 7.97 (d, 2H), 7.12–7.58 (m, 8H), 5.24 (d, 1H, *J* = 11.7 Hz), 4.64 (d, 1H, *J* = 11.7 Hz), 4.24 (q, 2H, *J* = 7.2 Hz), 4.10 (t, 2H, *J* = 6.3 Hz), 2.61 (m, 2 H), 2.22–2.46 (m, 4H), 1.61 (m, 2H), 1.10–1.40 (m, 13H), 0.88 (t, 3H, *J* = 5.0 Hz); ^{13}C NMR ($CDCl_3$)™ 171.62, 170.22, 169.72, 165.72, 140.65, 133.36, 129.89, 129.81, 128.72, 128.62, 128.58, 126.33, 85.96, 65.27, 61.92, 41.62, 35.14, 34.09, 33.49, 31.83, 31.76, 29.72, 29.22, 29.11, 25.13, 24.90, 22.79, 22.78, 14.35, 14.27, 14.24; IR (neat) 3389(b), 2935(s), 2852(s), 1745(s), 1727(s), 1684(s); CIMS (methane) *m/z*: 526.3 (M+H), 400.2, 382.2.
For **5d**: ^{1}H NMR ($CDCl_3$)™ 7.36 (s, 5 H), 6.31 (s, 1H), 5.26 (t, 1H, *J* = 5.0 Hz), 5.13 (s, 1H), 4.90 (d, 1H, *J* = 11.8 Hz), 4.37 (d, 1H, *J* = 11.8 Hz), 3.96 (t, 2H, *J* = 6.6 Hz), 2.52 (m, 1H), 2.19 (m, 1H), 1.95 (m, 1H), 1.58 (s, 2H), 1.37 (s, 9H), 1.24 (b, 10H), 1.13 (dd, 6H *J* = 7.0, 2.3 Hz), 0.86 (t, 3H, 6.3 Hz); ^{13}C NMR ($CDCl_3$)™ 176.60,

168.22, 167.72, 156.54, 136.17, 128.80, 128.55, 128.31, 87.53, 67.48, 64.48, 51.73, 43.70, 34.11, 32.11, 31.87, 29.44, 29.19, 28.82, 22.99, 22.78, 19.20, 19.11, 14.29; IR (neat) 3422(m), 3339(b). 2961(s), 2927(s), 2857(s), 1735(s), 1672(s); CIMS (methane) *m/z*: 521 (M+H), 413, 312.

For **5g**: ^{1}H NMR ($CDCl_3$)™ 8.05 (d, 2H, *J* = 5.0 Hz), 7.44–7.66 (m, 3H), 6.99 (t, 1H, *J* = 5.0 Hz), 5.26 (d, 1H, *J* = 11.5 Hz), 5.00 (d, 1H, *J* = 11.5 Hz), 4.24 (q, 2H, *J* = 7.2 Hz), 4.12 (dd, 2H, *J* = 3.5, 1.5 Hz), 3.40 (s, 2H), 2.46 (m, 1H), 1.75–1.88 (m, 4H), 1.10–1.40 (m, 9H); ^{13}C NMR ($CDCl_3$)™ 169.97, 169.34, 165.11, 162.50, 134.18, 130.25, 130.09, 129.27, 113.12, 88.23, 66.17, 62.20, 42.39, 41.82, 27.95, 27.59, 26.74, 26.61, 26.37, 25.02, 14.59; IR (neat) 3426(s), 2930(s), 2854(s), 1757(s), 1726(s), 1683(s); CIMS (methane) *m/z*: 445 (M+H), 360, 323.