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Dialkyl Diazomalonates in Transition-Metal-Free, Thermally Promoted, Diastereoselective Wolff β-Lactam Synthesis

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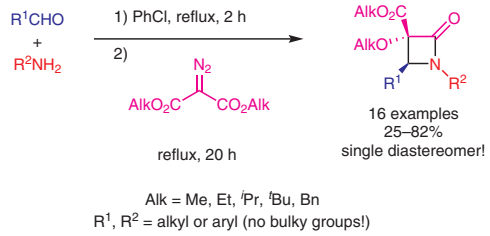

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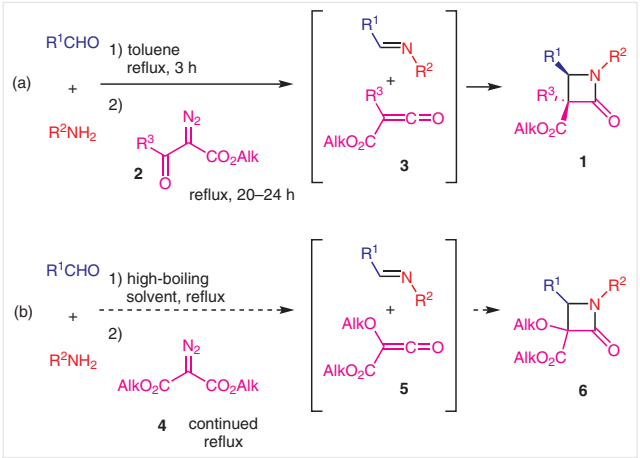
Abstract Metal-free, thermally promoted synthesis of 3-alkoxy-3-alkoxycarbonyl-2-azetidinones *via* the Wolff-Staudinger β-lactam synthesis using dialkyl diazomalonates is described. The reaction appears fairly general and delivers only one diastereomer.

Key words β-lactam, diazomalonates, Wolff rearrangement, metal-free, thermal

β-Lactams (2-azetidinones) can be confidently regarded as privileged motifs in drug design.[1] Recently, we described a one-pot, three component, generally diastereoselective synthesis of polysubstituted β-lactams **1** from in situ formed imines and readily available α-acyl-α-diazoacetate esters **2**.[2] The reaction essentially represented the first example of metal-free generation of specifically substituted ketenes **3** bearing an alkoxy carbonyl function via the thermally initiated[3] Wolff rearrangement (Scheme 1, a). Considering the obvious attractiveness of this metal-free approach to the earlier reported alternatives involving Rh(II) carbenes[4] and the general prominence of β-lactams in antibacterial drug design[5] (as well as other therapeutic areas[6]) we considered an opportunity to expand this methodology to include other types of readily available diazo compounds. In particular, dialkyl diazomalonates **4**, if found workable in the same atom-economic transformation (presumably, via the intermediacy of alkoxy-substituted ketenes **5**), would deliver 3-alkoxy-3-alkoxycabonyl-2-azetidinones **6** (Scheme 1, b).

The latter represent exceedingly rare type of substituted β-lactams. Several related representatives have been prepared from diazo Meldrum's acid *via* photolytically generated carbene[7] or Rh(II) carbene species[8] but have not been prepared in library fashion. Considering the high variability of the imine component, the ready commercial[9] and synthetic availability (*vide infra*) of dialkyl diazomalonates **4**, we set off to investigate their three-component, catalyst-free[10] reaction which would make the method particularly suitable for generating arrays of these compounds in diversity-controlled manner for subsequent biotarget interrogation.[6]



Scheme 1 The thermally promoted Wolff-Staudinger β-lactam synthesis (a) reported earlier[2] and (b) investigated in this work

There are a few isolated examples in the literature describing generation of ketenes **5** from diazomalonate derivatives **4** under photolytic[11] or gas-phase pyrolysis[12] conditions; however, these reports did not convey the synthetic utility of this transformation. In order to identify workable conditions that would lead to the envisioned transformation **4** → **6**, dimethyl diazomalonate (**4a**) was introduced into the solution of (*E*)-*N*-ethyl-1-(*p*-tolyl)methanimine (prepared in a separate step from *p*-tolualdehyde and ethylamine) in various highly boiling solvents at various ratios, temperatures, and time regimens (Table 1). Not unexpect-

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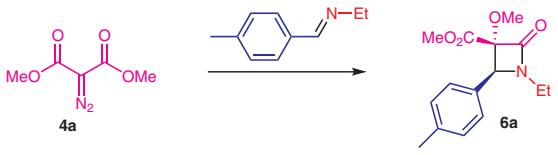
edly, dialkyl malonates **4** are more stable toward thermal decomposition compared to α-acyl-α-diazoacetate esters **2** and, thus, prolonged (20 h) reflux in toluene (Table 1, entry 1) only led to incomplete conversion. Switching to xylene (Table 1, entry 2) and to chlorobenzene (Table 1, entry 3) using only 1.1 equiv of **4a** led to some improvement of the yield of the target product **6a**. However, the optimal isolated yield of **6a** (65% of a single diastereomer) was achieved with 2 equiv of **4a** (Table 1, entry 5), and these conditions were adopted to study the reaction scope using dialkyl diazomalonates **4a–e** conveniently prepared on multigram scale from respective dialkyl malonates using the previously described SAFE diazo transfer procedure,[13] except for the sterically hindered **4d** which required using a different diazo transfer reagent (Figure 1).[14]

Table 1 Conditions Finding for the Preparation of **6a**



Entry	**4a** (equiv)	Solvent	Temp (°C)	Time (h)	Yield of **6a** (%)
1	1.1	toluene	110	20	<20% conversion
2	1.1	xylene	150	6	24
3	1.1	PhCl	130	16	38
4	1.5	PhCl	130	20	51
5	2.0	PhCl	130	20	65
6	3.0	PhCl	130	20	63

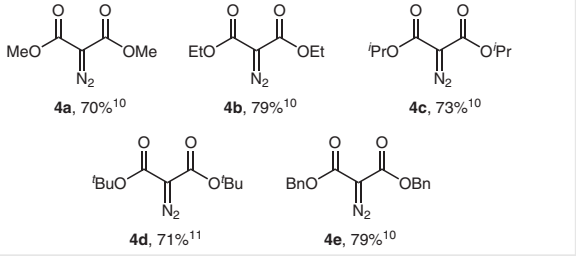


Figure 1 Dialkyl diazomalonates **4a–e** employed in this work

In the majority of cases, the amine and the aldehyde were combined in equimolar amounts in chlorobenzene, refluxed with $CaCl_2$ tube serving as a condenser for 2 h to ensure the complete formation of the intermediate imine, whereupon dialkyl diazomalonate was introduced and the refluxing continued for 20 h.[15] In some cases, however, imine was either preformed due to volatility of one of the reaction components or because it was available off-the-shelf at the time. The structures and yields of the β-lactam products (obtained as the single diastereomer shown in all cases, with no signals from the opposite diastereomer detectable in the crude ^{1}H NMR spectrum) are provided in Scheme 2.[16] The origin[17] of the observed excellent diastereoselectivity is likely similar to the one previously rationalized for the generally diastereoselective formation of lactams **1**.[2] The relative stereochemistry, corresponding to the *trans* relationship between the R group and the alkoxy substituent was confirmed by the single-crystal X-ray analysis of the representative compound **6i** (Figure 2).

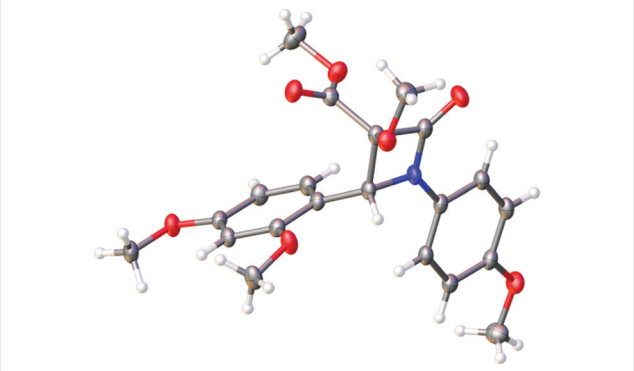


Figure 2 Single-crystal X-ray structure of compound **6i** (CCDC1975681, thermal ellipsoids are shown at 50% probability; see Supporting Information for details)

As to the reactivity pattern illustrated by examples in Scheme 2, migration of the *tert*-butoxy substituent preceding the formation of the ketene intermediate appears to be least efficient (cf. compound **6o**), likely for steric reasons. Steric bulk is the likely reason for no product **6k** obtained with *tert*-butylamine (same result was observed for lactams **1**[2]). Electron-withdrawing groups in the aldehyde portion appear to be disfavored (compare **6p** with **6q** as well as **6g**).

In conclusion, we have described the first metal-free, thermally promoted synthesis of 3-alkoxy-3-alkoxycarbonyl-2-azetidinones *via* the Wolff β-lactam synthesis using dialkyl diazomalonates. The reaction appears fairly general and displays remarkable diastereoselectivity. The compounds obtained are exceedingly rare in the public domain while belonging to the privileged β-lactam class. Being able to prepare them in diversity-controlled, library format will undoubtedly promote and facilitate their biological annotation.

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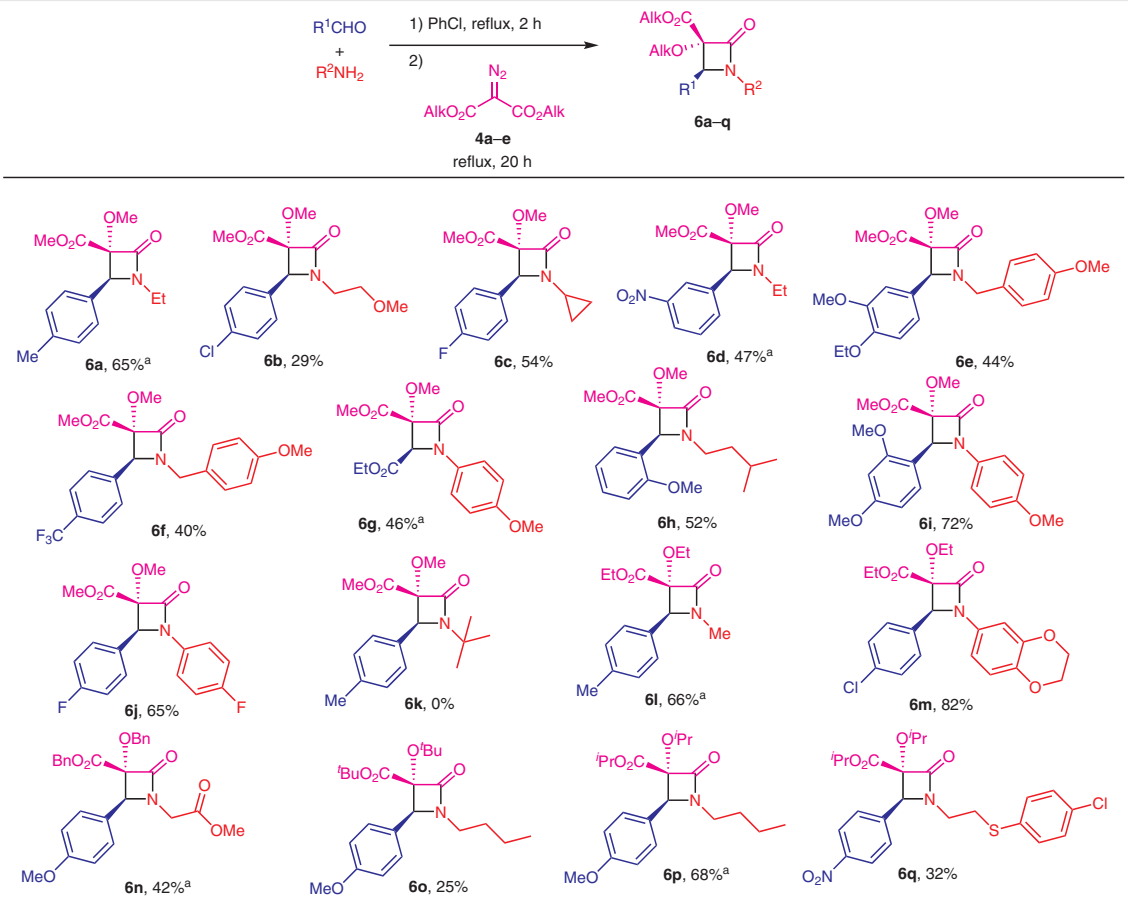

Scheme 2 Synthesis of racemic β-lactams **6a–q**.[15,16] [a] Reaction was conducted with a preformed imine.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707811.

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(15) **General Procedure for the Preparation of Lactams 6a–p**
In a 25 mL round-bottom flask, amine (0.8 mmol, 1.0 equiv) and aldehyde (0.9 mmol, 1.1 equiv) were dissolved in 10 mL of chlorobenzene and refluxed with azeotropic removal of water. After 1 h, half of the solvent was distilled off and 2-diazomalonates **4a–e** (1.6 mmol, 2.0 equiv) was added. The mixture was then refluxed overnight, and the reaction progress was followed *via* TLC. When no more diazo compound was detectable (20–24 h), the solvent was evaporated *in vacuo*, and the resulting mixture was purified by column chromatography on silica gel with a

linear gradient (0–20%) of acetone in *n*-hexane (total volume of eluent, 450 mL) to provide pure compounds **6a–p**. In case of volatile aldehyde or amine, they were reacted in chlorobenzene at room temperature overnight in the presence of 4 Å MS. The latter was filtered off before proceeding with the addition of **4** and heating. Compounds **6a**,**d**,**g**,**l**,**n**,**p** were prepared with the use of presynthesized imines.

(16) **Characterization Data of Representative Compounds**

Compound **6i**: white powder (231 mg, 72%); mp 113–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.9 Hz, 2 H), 6.95 (d, *J* = 8.5 Hz, 1 H), 6.87–6.82 (m, 2 H), 6.49 (d, *J* = 2.4 Hz, 1 H), 6.35 (d, *J* = 8.5 Hz, 1 H), 5.50 (s, 1 H), 3.89 (s, 3 H), 3.78 (d, *J* = 2.0 Hz, 6 H), 3.75 (s, 3 H), 3.39 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.3, 161.2, 161.1, 158.6, 156.5, 130.5, 128.6, 119.0, 114.4, 112.4, 104.0, 98.5, 94.5, 60.1, 55.9, 55.8, 55.5, 55.3, 51.9 ppm. HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{21}H_{23}NaNO_7$: 424.1367; found: 424.1378.

Compound **6l**: yellow powder (202 mg, 66%); mp 97–99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.7 Hz, 2 H), 7.01–6.68 (m, 2 H), 4.63 (s, 1 H), 4.08 (dq, *J* = 8.9, 7.0 Hz, 1 H), 3.92 (dq, *J* = 10.8, 7.1 Hz, 1 H), 3.81 (s, 3 H), 3.78–3.63 (m, 1 H), 2.93 (s, 3 H), 1.30 (t, *J* = 7.0 Hz, 3 H), 0.99 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.3, 165.0, 160.1, 128.6, 124.4, 113.9, 95.2, 67.8, 64.1, 61.4, 55.3, 27.4, 15.4, 13.8 ppm. HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{23}H_{27}NNaO_7$: 452.1680; found: 452.1683.

Compound **6n**: yellow oil (206 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.46 (m, 2 H), 7.42–7.26 (m, 8 H), 7.24–7.01 (m, 2 H), 6.80 (d, *J* = 8.0 Hz, 2 H), 5.35–5.09 (m, 2 H), 4.94 (d, *J* = 12.2 Hz, 1 H), 4.86–4.77 (m, 2 H), 4.54 (d, *J* = 18.0 Hz, 1 H), 3.81 (s, 3 H), 3.74 (s, 3 H), 3.65 (d, *J* = 18.0 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.9, 165.9, 164.8, 160.2, 137.0, 134.7, 128.6, 128.4, 128.4, 128.3, 128.2, 128.0, 123.6, 114.1, 95.7, 70.3, 67.1, 66.4, 55.2, 52.5, 41.3 ppm. HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{28}H_{27}NNaO_7$: 512.1680; found: 512.1700.

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