Leuckart Reductive Amination of a 4-Acetylazetidinone using Microwave Technology

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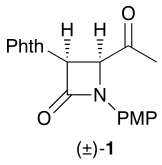
A microwave-mediated rate acceleration was observed during the reductive amination of a 4-acetylazetidinone.

As reported earlier by our group.[3] the Leuckart reductive amination of simple carbonyl compounds is widely enhanced, taking advantage of both focused microwave irradiation[8] and solvent-free techniques. We now have found that such techniques can also be applied to the representative 4-acetyl β-lactam **1** affording a 73% isolated yield of the expected 4-[1-(*N*-formylamino)ethyl]azetidin-2-ones **4**, **5** and **6** (in 55:20:25 molar ratio) within 20 min using as aminoformylating agent a mixture of 15 equivalents of formamide and 10 equivalents ofó formic acid (entry 5). A clearly beneficial microwave-specific effect (non-purely thermal) is evidenced as, under identical conditions, yields of final products are less and decomposition is enhanced (entry 6).

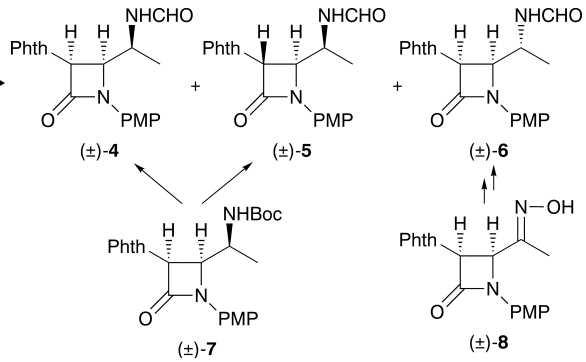


(±)-**1**

2 = $HCONH_2$
3 = HCO_2H

Entry	**1**:**2**:**3**	Time (*t*/min)	Temp. (*T*/°C)	Conversion (%)	Yield (%) **4**+**5**+**6**
1	(MW)1:5:5	20	143	25	0[a]
2	(MW)1:10:10	20	155	59	56[a]
3	(MW)1:10:10	30	156	83	83[a]
4	(MW)1:10:15	20	173	72	55[a]
5	(MW)1:15:10	20	180	99	93[a], 73[b]
6	(Δ)1:15:10	20	180	18	70[a]

PMP = 4-methoxyphenyl; Phth = phthalimido; MW = microwave; Δ = thermal. [a]GLC yield. [b]Isolated yield.



(±)-**4** (±)-**5** (±)-**6** (±)-**7** (±)-**8**

The stereochemistry of **4**, **5** and **6** was ascertained by their alternative synthesis from the β-lactam **7**[4] and oxime **8** (prepared from **1**). Thus, the β-lactam **7** could be cleanly transformed into the 4-(1-*N*-formylamino)ethyl analogue **4** by stepwise deprotection of the *N*-Boc group with trifluoroacetic acid followed by formylation with formic-acetic mixed anhydride.[5] Conversely, the β-lactam **7** was enolized exclusively at the C-3 position[6] with lithium bis(trimethylsilyl)-amide and protonated to give the *trans*,*syn*-epimer, which was subjected to *N*-Boc deprotection and *N*-formylation as above, affording a compound which was spectroscopically identical with **5**.

Finally, the non-stereoselective reduction of the oxime **8** with aluminium–nickel alloy, according to Krimen's method,[7] led to a mixture of *cis*,*syn*- and *cis*,*anti*-4-(1-aminoethyl)-β-lactams, which was subjected to formylation, giving a 60:40 mixture of β-lactams **4** and **6** from which the latter could be separated by preparative HPLC affording a compound identical with that obtained during the Leuckart reductive amination of **1**.

Techniques used: ^{1}H and ^{13}C NMR, IR, GLC, HPLC, column chromotography

References: 10

Figures: 1

Schemes: 2

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References cited in this synopsis

3 A. Loupy, D. Monteux, A. Petit, J. M. Aizpurua, E. Domínguez and C. Palomo, *Tetrahedron Lett*., 1996, **37**, 8177.
4 C. Palomo, F. P. Cossio, C. Cuevas, B. Lecea, A. Mielgo, P. Roman, A. Luque and M. Martinez-Ripoll, *J. Am. Chem. Soc*., 1992, **114**, 9360.
5 J. C. Sheehan and D.-D. H. Yang, *J. Am. Chem. Soc*., 1958, **80**, 1154.
6 I. Ojima, in *The Organic Chemistry of β-Lactams*, ed. G. I. Georg, VCH, Weinheim, 1992, 197.
7 L. I. Krimen, *Org. Synth*., 1970, **50**, 1.
8 A Synthewave 402 reactor from Prolabo (94126 Fontenay-sous-Bois, France) was used with a focused microwave system and infrared detection of temperature under continuous stirring: R. Commarmot, R. Dodenot and J. F. Gardais, Prolabo, *Fr. Pat*. 84/03496, 1986; P. Jacquault, Prolabo, *Fr. Pat*. 549495 AJ, 1992.