Parallel Kinetic Resolution of N-Heterocycles by N-Acylations in Flow

Significance: A flow system for parallel kinetic resolution of N-heterocycles by using polymer-supported pseudoenantiomeric acylating agents was developed. A racemic mixture of heterocycles 1 was converted into the corresponding enantiomer-enriched amides 4 and 5 in 17–50% yield by using a flow-reaction system with acylating agents 2 and 3 (0.5 mol equiv each).

Comment: The resulting amides 4 and 5 were readily deprotected to give the corresponding free amines. Thus, for example, (R,S)- and (S,R)-mefloquine (1e) were obtained from a 1:1 mixture of amides 4e and 5e by selective deprotection without detectable epimerization (60–90% yield).

Selected examples:

- 4a: 50% yield (er = 95:5)
- 4b: 45% yield (er = 89:11)
- 4c: 28% yield (er = 96:4)
- 4d: 40% yield (er = 97:3)
- 4e: 18% yield (er = 94:6)

- 5a: 48% yield (er = 93:7)
- 5b: 35% yield (er = 95:5)
- 5c: 35% yield (er = 94:6)
- 5d: 48% yield (er = 96:4)
- 5e: 17% yield (er = 96:4)

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Synfacts 2017, 13(08), 0877 Published online: 18.07.2017
DOI: 10.1055/s-0036-1590709; Reg-No.: Y09317SF