2-Oxazol-5-ylethanones by Consecutive Three-Component Amidation–Coupling–Cycloisomerization (ACCI) Sequence

Eugen Merkul, Oliver Grotkopp, Thomas J. J. Müller*

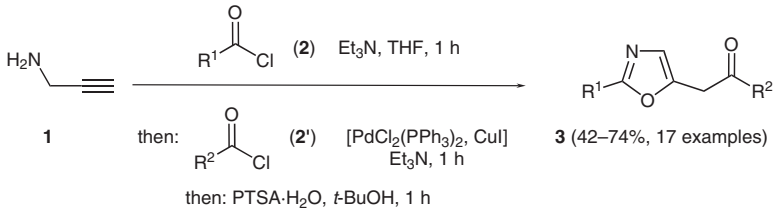
Lehrstuhl für Organische Chemie, Institut für Organische Chemie und Makromolekulare Chemie, Heinrich-Heine-Universität Düsseldorf, Universitätsstraße 1, 40225 Düsseldorf, Germany
Fax +49(211)8114324; E-mail: ThomasJJ.Mueller@uni-duesseldorf.de

Received 4 September 2008; revised 5 September 2008

PSP No 145

Abstract: Substituted oxazol-5-ylethanones can be synthesized in a consecutive three-component sequence starting from propargylamine and various acid chlorides, both for amidation and cross-coupling. Therefore, this diversity-oriented one-pot approach to substituted oxazoles can be considered as an amidation-coupling-cycloisomerization (ACCI) sequence.

Key words: C–C coupling, catalysis, cycloisomerization, multi-component reactions, oxazoles



Scheme 1

Introduction

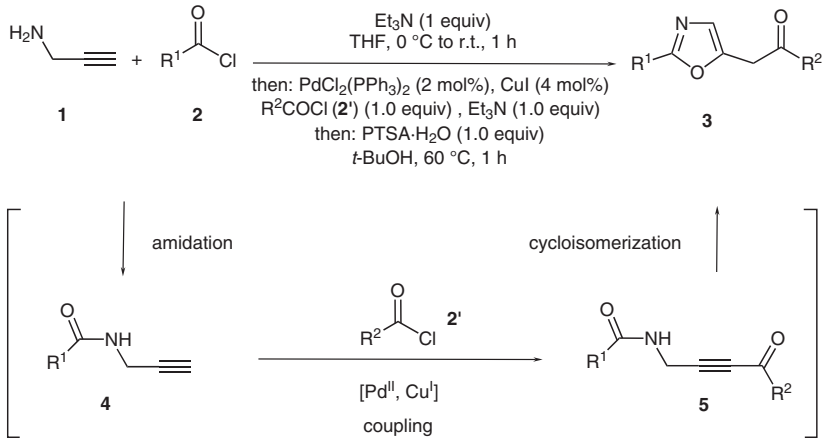
Oxazoles are prevalent substructures in natural products, synthetic intermediates, and pharmaceuticals.[1–3] Interestingly, many macrocyclic derivatives either from bacteria or from marine organisms containing oxazole units are highly cytotoxic, antitubuline, and antitumor active.[4] But even simpler structures such as oxazolyl acetic acid and their (hetero)aromatic derivatives have been shown to be antipyretic and antihyperglycemic.[5] Besides the Robinson–Gabriel synthesis,[6,7] that is, the cyclocondensation of α-acylamino ketones with strongly dehydrating agents, milder methods for the preparation of highly functionalized oxazoles are still highly desirable.[8] In particular, propargyl amides undergo cycloisomerization to 2,5-disubstituted oxazoles by acid or base catalysis, by palladium-catalyzed coupling of aryl iodides in the presence of sodium *tert*-butoxide,[9] or by gold catalysis.[10] Recently, as part of our program directed to develop new one-pot multi-component heterocycle syntheses initiated by alkyne coupling,[11] we have disclosed a novel one-pot three-component synthesis of substituted oxazol-5-ylethanones **3** (Scheme 1).[12] This three-component methodological extension of Wipf's elegant synthesis of the structural motif[13] commences with the amidation of propargylamine (**1**) with acid chlorides **2**, followed by Sonogashira alkynylation of the acid chlorides **2′** with the propargyl amides **4** to give the alkynones **5** (Scheme 2).[12] By addition of one equivalent of *p*-toluenesulfonic acid monohydrate (PTSA·H_2O) and *tert*-butyl alcohol to the reaction mixture and gentle heating, alkynones **5** cycloisomerize to furnish the substituted oxazol-5-ylethanones **3** (Scheme 2).

Scope and Limitation

Methodologically, the one-pot three-component ACCI synthesis of substituted oxazol-5-ylethanones **3** proceeds efficiently under mild conditions with a wide variety of electronically diverse acid chlorides (Table 1). In addition, acid chlorides with halogens (Table 1, entries 4, 6–9), alkenes (entries 13, 15–17), and heterocycles (entries 5, 11, 12, 14) as substituents can be carried through the sequence without interference. However, the major advantage of this procedure is the use of only equimolar amounts of reactants and additives. All this renders the one-pot process very economic and rapid (3 h).

In summary, the consecutive three-component amidation–coupling–cycloisomerization (ACCI) synthesis of substituted oxazol-5-ylethanones opens a straightforward, economical access to oxazoles and can serve as an entry to more complex substituted heterocycles by oxazole transformations.

SYNTHESIS 2009, No. 3, pp 0502–0507
Advanced online publication: 19.12.2008
DOI: 10.1055/s-0028-1083294; Art ID: Z20508SS



Scheme 2 One-pot three-component synthesis of substituted oxazol-5-ylethanones and mechanistic rationale

Table 1 One-Pot Three-Component Synthesis of Substituted Oxazol-5-ylethanones **3**

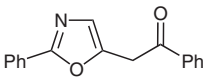
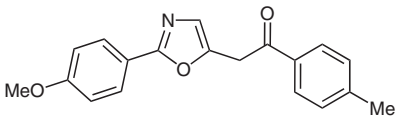
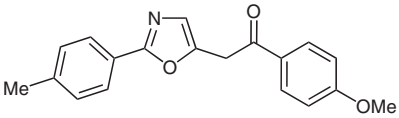
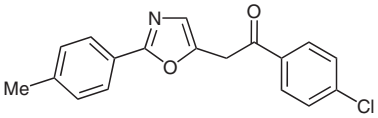
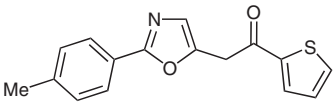
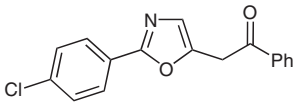
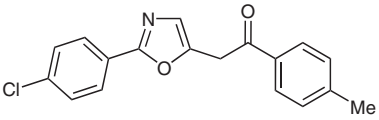
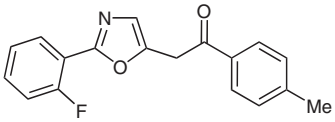
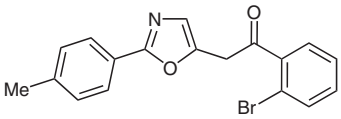
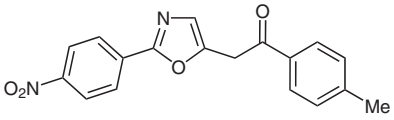
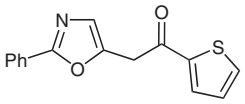
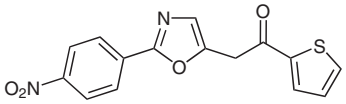
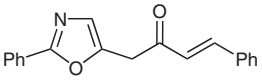
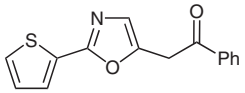
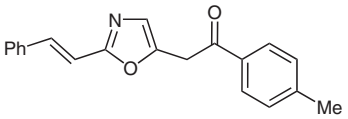
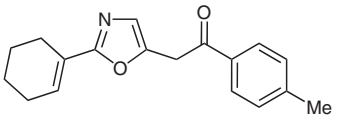
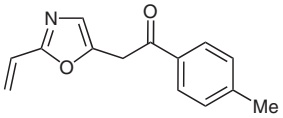
Entry	First acid chloride		Second acid chloride		Oxazole product		Yield
	2	R^1	**2′**	R^2	**3**		(%)
1	**2a**	Ph	**2a′**	Ph	**3a**		70
2	**2b**	4-$MeOC_6H_4$	**2c′**	4-MeC_6H_4	**3b**		58
3	**2c**	4-MeC_6H_4	**2b′**	4-$MeOC_6H_4$	**3c**		72
4	**2c**	4-MeC_6H_4	**2d′**	4-ClC_6H_4	**3d**		74
5	**2c**	4-MeC_6H_4	**2e′**	2-thienyl	**3e**		73
6	**2d**	4-ClC_6H_4	**2a′**	Ph	**3f**		75
7	**2d**	4-ClC_6H_4	**2c′**	4-MeC_6H_4	**3g**		59
8	**2f**	2-FC_6H_4	**2c′**	4-MeC_6H_4	**3h**		68
9	**2c**	4-MeC_6H_4	**2g′**	2-BrC_6H_4	**3i**		50

Table 1 One-Pot Three-Component Synthesis of Substituted Oxazol-5-ylethanones **3** (continued)

Entry	First acid chloride		Second acid chloride		Oxazole product		Yield
	2	R^1	**2′**	R^2	**3**		(%)
10	**2h**	4-$O_2NC_6H_4$	**2c′**	4-MeC_6H_4	**3j**		68
11	**2a**	Ph	**2e′**	2-thienyl	**3k**		53
12	**2h**	2-$O_2NC_6H_4$	**2e′**	2-thienyl	**3l**		56
13	**2a**	Ph	**2i′**	2-styryl	**3m**		49
14	**2e**	2-thienyl	**2a′**	Ph	**3n**		70
15	**2i**	2-styryl	**2c′**	4-MeC_6H_4	**3o**		66
16	**2j**	cyclohexen-1-yl	**2c′**	4-MeC_6H_4	**3p**		57
17	**2k**	ethenyl	**2c′**	4-MeC_6H_4	**3q**		42

All reactions involving water-sensitive compounds were carried out in oven-dried Schlenk glassware under argon or nitrogen. THF and Et_3N were dried with ketylsodium according to standard procedures[14] and were distilled prior to use. Column chromatography: silica gel 60 M (mesh 230–400) Macherey-Nagel. TLC: silica gel layered aluminum foil (60 F_{254} Merck, Darmstadt). Melting points (uncorrected): Reichert-Jung Thermovar and Büchi Melting Point B-540. Propargylamine (**1**) and acid chlorides **2**, PTSA·H_2O, $PdCl_2(PPh_3)_2$, and CuI were purchased from ACROS, Aldrich Chemie GmbH, Fluka AG, Lancaster AG, or Merck KGaA and used without further purification. ^1H and ^{13}C NMR spectra: Bruker ARX250, Bruker DRX 300, Bruker DRX 300 or Bruker DRX 500 with $CDCl_3$ as solvent. The assignments of quaternary C, CH, CH_2, and CH_3 were made on the basis of DEPT spectra. MS: Jeol JMS-700 und Finnigan TSQ 700. Elemental analyses were carried out in the microanalytical laboratory of the Organisch-Chemisches Institut der Universität Heidelberg and in the microanalytical laboratory of the Pharmazeutisches Institut of the Heinrich-Heine-Universität Düsseldorf.

2-Oxazol-5-ylethanones; General Procedure

To a solution of propargylamine (**1**; 56 mg, 1.00 mmol) in anhyd degassed THF (5 mL) in a flame-dried screw-cap vessel under argon were successively added acid chloride **2** (1.00 mmol) and Et_3N (0.14 mL, 1.00 mmol) at 0 °C (external cooling with ice-water) (for experimental details see Table 1). After stirring for 1 h at r.t., a colorless to pale yellow precipitate formed. Then, $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), CuI (8 mg, 0.04 mmol), acid chloride **2′** (1.00 mmol), and Et_3N (0.14 mL, 1.00 mmol) were successively added to the reaction mixture and the stirring was continued for 1 h at r.t. Then, to the brown mixture PTSA·H_2O (190 mg, 1.00 mmol) and *t*-BuOH (1 mL) were added and the stirring was continued for 1 h at 60 °C. After cooling to r.t., brine (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and after evaporation of the solvents the residue was chromatographed on silica gel with hexanes–EtOAc as eluent in variable ratios to give the analytically pure 1-(hetero)aryl-2-oxazol-5-ylethanones **3**.

3a[13]

Acid chlorides **2a** (141 mg, 1.00 mmol) and **2a′** (141 mg, 1.00 mmol) were used according to the general procedure to produce 185 mg (70%) of **3a** as a colorless amorphous solid; mp 84–85 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.43 (s, 2 H), 7.14 (s, 1 H), 7.39–7.55 (m, 5 H), 7.57–7.65 (m, 1 H), 7.96–8.06 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.0, 126.2, 126.9 127.5, 128.5, 128.7, 128.8, 130.2, 133.7, 135.9, 145.5, 161.6, 193.7.

3b

Acid chlorides **2b** (171 mg, 1.00 mmol) and **2c′** (158 mg, 1.00 mmol) were used according to the general procedure to produce 179 mg (58%) of **3b** as light yellow needles; mp 88 °C (CH_2Cl_2–pentane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 3.84 (s, 3 H), 4.38 (s, 2 H), 6.94 (d, *J* = 8.8 Hz, 2 H), 7.06 (s, 1 H), 7.29 (d, *J* = 7.9 Hz, 2 H), 7.90–7.96 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 35.9, 55.4, 114.1, 120.4, 126.5, 127.9, 128.6, 129.5, 133.5, 144.6, 145.1, 161.2, 161.6, 193.5.

Anal. Calcd for $C_{19}H_{17}NO_3$ (307.3): C, 74.25; H, 5.58; N, 4.56. Found: C, 74.02; H, 5.58; N, 4.55.

3c

Acid chlorides **2c** (158 mg, 1.00 mmol) and **2b′** (171 mg, 1.00 mmol) were used according to the general procedure to produce 222 mg (72%) of **3c** as a yellow solid; mp 95 °C (CH_2Cl_2–pentane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.39 (s, 3 H), 3.88 (s, 3 H), 4.38 (s, 2 H), 6.97 (d, *J* = 9.0 Hz, 2 H), 7.13 (s, 1 H), 7.24 (d, *J* = 8.0 Hz, 2 H), 7.91 (d, *J* = 8.2 Hz, 2 H), 8.01 (d, *J* = 8.9 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.5, 34.7, 54.7, 113.0, 123.2, 124.8, 125.3, 127.9, 128.5, 129.8, 139.9, 144.7, 160.7, 163.0, 191.1.

Anal. Calcd for $C_{19}H_{17}NO_3$ (307.3): C, 74.25; H, 5.58; N, 4.56. Found: C, 74.04; H, 5.61; N, 4.66.

3d

Acid chlorides **2c** (158 mg, 1.00 mmol) and **2d′** (177 mg, 1.00 mmol) were used according to the general procedure to produce 232 mg (74%) of **3d** as light beige platelets; mp 139 °C (CH_2Cl_2–pentane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (s, 3 H), 4.39 (s, 2 H), 7.10 (s, 1 H), 7.24 (d, *J* = 8.3 Hz, 2 H), 7.48 (d, *J* = 8.3 Hz, 2 H), 7.88 (d, *J* = 8.3 Hz, 2 H), 7.97 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 36.0, 124.7, 126.2, 126.8, 129.2, 129.5, 129.9, 134.2, 140.3, 140.6, 144.7, 161.9, 192.6.

Anal. Calcd for $C_{18}H_{14}ClNO_2$ (311.8): C, 69.35; H, 4.53; N, 4.49; Cl, 11.37. Found: C, 69.42; H, 4.59; N, 4.49; Cl, 11.16.

3e

Acid chlorides **2c** (158 mg, 1.00 mmol) and **2e′** (150 mg, 1.00 mmol) were used according to the general procedure to produce 205 mg (73%) of **3e** as brown crystals; mp 104 °C (CH_2Cl_2–pentane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.39 (s, 3 H), 4.35 (s, 2 H), 7.13 (s, 1 H), 7.17 (m, 1 H), 7.24 (d, *J* = 8.3 Hz, 2 H), 7.71 (dd, *J* = 1.0, 4.9 Hz, 1 H), 7.83 (dd, *J* = 1.0, 3.8 Hz, 1 H), 7.91 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.9, 37.1, 124.8, 126.7, 126.7, 128.8, 129.9, 133.3, 135.2, 141.2, 143.3, 145.2, 162.3, 186.8.

Anal. Calcd for $C_{16}H_{13}NO_2S$ (283.3): C, 67.82; H, 4.62; N, 4.94. Found: C, 67.63; H, 4.56; N, 5.04.

3f

Acid chlorides **2d** (177 mg, 1.00 mmol) and **2a′** (141 mg, 1.00 mmol) were used according to the general procedure to produce 225 mg (75%) of **3f** as colorless platelets; mp 128–129 °C (CH_2Cl_2–pentane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.44 (d, *J* = 0.7 Hz, 2 H), 7.14 (s, 1 H), 7.40 (d, *J* = 8.7 Hz, 2 H), 7.47–7.55 (m, 2 H), 7.62 (tt, *J* = 2.1, 7.3 Hz, 1 H), 7.93 (d, *J* = 8.7 Hz, 2 H), 8.00–8.06 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.9, 126.8, 127.5, 127.9, 128.1, 128.5, 128.8, 130.1, 133.8, 135.9, 145.0, 157.8, 193.6.

Anal. Calcd for $C_{17}H_{12}ClNO_2$ (297.7): C, 68.58; H, 4.06; N, 4.70; Cl, 11.91. Found: C, 68.21; H, 4.02; N, 4.68; Cl, 12.12.

3g

Acid chlorides **2d** (177 mg, 1.00 mmol) and **2c′** (158 mg, 1.00 mmol) were used according to the general procedure to produce 183 mg (59%) of **3g** as colorless platelets; mp 138 °C (CH_2Cl_2–pentane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 4.42 (s, 2 H), 7.17 (s, 1 H), 7.31 (d, *J* = 7.9 Hz, 2 H), 7.42 (d, *J* = 8.7 Hz, 2 H), 7.86 (d, *J* = 8.2 Hz, 2 H), 7.91 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2, 36.2, 125.8, 126.7, 128.1, 129.0, 129.6, 130.0, 133.7, 137.1, 145.3, 146.7, 161.1, 193.4.

Anal. Calcd for $C_{18}H_{14}ClNO_2$ (311.8): C, 69.35; H, 4.53; N, 4.49. Found: C, 69.27; H, 4.67; N, 4.37.

3h

Acid chlorides **2f** (159 mg, 1.00 mmol) and **2c′** (158 mg, 1.00 mmol) were used according to the general procedure to produce 202 mg (68%) of **3h** as colorless thin platelets; mp 88 °C (CH_2Cl_2–pentane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 4.43 (d, *J* = 1.3 Hz, 2 H), 7.13–7.25 (m, 3 H), 7.30 (d, *J* = 7.9 Hz, 2 H), 7.36–7.45 (m, 1 H), 7.94 (d, *J* = 8.3 Hz, 2 H), 7.96–8.03 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 35.9, 115.8 (d, *J* = 11.1 Hz), 116.8 (d, *J* = 22.1 Hz), 124.3 (d, *J* = 4.2 Hz), 126.9, 128.6, 129.5, 129.5 (d, *J* = 9.7 Hz), 131.7 (d, *J* = 8.3 Hz), 133.5, 144.7, 146.1, 157.8 (d, *J* = 4.2 Hz), 159.9 (d, *J* = 257.4 Hz), 193.2.

Anal. Calcd for $C_{18}H_{14}FNO_2$ (295.3): C, 73.21; H, 4.78; N, 4.74. Found: C, 73.42; H, 4.79; N, 4.77.

3i

Acid chlorides **2c** (158 mg, 1.00 mmol) and **2g′** (220 mg, 1.00 mmol) were used according to the general procedure to produce 178 mg (50%) of **3i** as brown columns; mp 86 °C (CH_2Cl_2–pentane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (s, 3 H), 4.40 (d, *J* = 1.0 Hz, 2 H), 7.08 (s, 1 H), 7.24 (d, *J* = 7.5 Hz, 2 H), 7.27–7.47 (m, 3 H), 7.60–7.65 (m, 1 H), 7.87 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 39.6, 118.8, 124.7, 126.2, 126.9, 127.6, 128.9, 129.4, 132.1, 133.8, 140.5, 140.5, 144.3, 161.9, 197.8.

Anal. Calcd for $C_{18}H_{14}BrNO_2$ (356.2): C, 60.69; H, 3.96; N, 3.93; Br, 22.43. Found: C, 60.68; H, 3.99; N, 3.98; Br, 22.26.

3j

Acid chlorides **2h** (186 mg, 1.00 mmol) and **2c′** (158 mg, 1.00 mmol) were used according to the general procedure to produce 220 mg (68%) of **3j** as a yellow solid; mp 190 °C (dec., CH_2Cl_2–pentane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 4.46 (s, 2 H), 7.23 (s, 1 H), 7.32 (d, *J* = 8.3 Hz, 2 H), 7.94 (d, *J* = 8.3 Hz, 2 H), 8.16 (d, *J* = 8.8 Hz, 2 H), 8.30 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8, 35.8, 124.2, 126.9, 127.9, 128.6, 129.6, 132.9, 133.3, 145.0, 147.6, 148.5, 159.5, 192.9.

Anal. Calcd for $C_{18}H_{14}N_2O_4$ (322.3): C, 67.08; H, 4.38; N, 8.69. Found: C, 66.69; H, 4.35; N, 8.66.

3k

Acid chlorides **2a** (141 mg, 1.00 mmol) and **2e′** (150 mg, 1.00 mmol) were used according to the general procedure to produce 143 mg (53%) of **3k** as a yellow solid; mp 118 °C (CH_2Cl_2–pentane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.36 (d, *J* = 0.8 Hz, 2 H), 7.14 (s, 1 H), 7.17 (dd, *J* = 3.8, 4.9 Hz, 1 H), 7.40–7.46 (m, 3 H), 7.70 (dd, *J* = 1.1, 5.1 Hz, 1 H), 7.83 (dd, *J* = 1.1, 3.8 Hz, 1 H), 7.97–8.03 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.7, 126.2, 126.9, 127.4, 128.4, 128.7, 130.2, 132.9, 134.8, 142.9, 145.1, 161.7, 186.4.

HRMS: *m*/*z* calcd for $C_{15}H_{11}NO_2S$: 269.0510; found: 269.0490.

3l

Acid chlorides **2h** (186 mg, 1.00 mmol) and **2e′** (150 mg, 1.00 mmol) were used according to the general procedure to produce 177 mg (56%) of **3l** as an orange solid; mp 167 °C (CH_2Cl_2–pentane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.40 (d, *J* = 0.8 Hz, 2 H), 7.18 (dd, *J* = 3.8, 4.9 Hz, 1 H), 7.23 (t, *J* = 0.8 Hz, 1 H), 7.72 (d, *J* = 1.1, 4.9 Hz, 1 H), 7.83 (d, *J* = 1.1, 3.8 Hz, 1 H), 8.14 (d, *J* = 8.7 Hz, 2 H), 8.27 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.9, 124.6, 127.3, 128.2, 128.9, 133.0, 133.4, 135.5, 143.1, 147.3, 149.0, 156.0, 186.3.

Anal. Calcd for $C_{15}H_{10}N_2O_4S$ (314.3): C, 57.32; H, 3.21; N, 8.91. Found: C, 57.26; H, 3.04; N, 8.79.

3m[13]

Acid chlorides **2a** (141 mg, 1.00 mmol) and **2i′** (170 mg, 1.00 mmol) were used according to the general procedure to produce 143 mg (49%) of **3m** as a yellow solid; mp 97 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.09 (s, 2 H), 6.84 (d, *J* = 15.8 Hz, 1 H), 7.13 (s, 1 H), 7.35–7.48 (m, 6 H), 7.52–7.58 (m, 2 H), 7.70 (d, *J* = 15.8 Hz, 1 H), 7.98–8.05 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.4, 124.3, 126.2, 126.7, 127.4, 128.5, 128.7, 129.0, 130.2, 130.9, 134.0, 144.4, 145.5, 161.7, 193.3.

3n

Acid chlorides **2e** (150 mg, 1.00 mmol) and **2a′** (141 mg, 1.00 mmol) were used according to the general procedure to produce 190 mg (70%) of **3n** as a brown solid; mp 108 °C (EtOAc–pentane).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.42 (s, 2 H), 7.06–7.11 (m, 2 H), 7.39 (d, *J* = 4.9 Hz, 1 H), 7.51 (t, *J* = 7.7 Hz, 2 H), 7.59–7.64 (m, 2 H), 8.03 (d, *J* = 7.7 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 35.9, 126.8, 127.5, 127.9, 128.1, 128.5, 128.8, 130.1, 133.8, 135.9, 145.0, 157.8, 193.6.

HRMS: *m*/*z* calcd for $C_{15}H_{11}NO_2S$: 269.0510, found: 269.0502.

3o

Acid chlorides **2i** (170 mg, 1.00 mmol) and **2c′** (158 mg, 1.00 mmol) were used according to the general procedure to produce 200 mg (66%) of **3o** as a yellow solid; mp 101 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 4.37 (d, *J* = 0.9 Hz, 2 H), 6.91 (d, *J* = 16.2 Hz, 1 H), 7.07 (s, 1 H), 7.26–7.41 (m, 5 H), 7.44 (d, *J* = 16.7 Hz, 1 H), 7.48–7.53 (m, 2 H), 7.92 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 35.9, 114.0, 126.9, 127.1, 128.6, 128.8, 129.1, 129.5, 133.4, 135.6, 135.6, 144.7, 145.4, 161.4, 193.3.

Anal. Calcd for $C_{20}H_{17}NO_2$ (303.4): C, 79.19; H, 5.65; N, 4.62. Found: C, 78.96; H, 5.65; N, 4.57.

3p

Acid chlorides **2j** (145 mg, 1.00 mmol) and **2c′** (158 mg, 1.00 mmol) were used according to the general procedure to produce 161 mg (57%) of **3p** as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.59–1.77 (m, 4 H), 2.16–2.25 (m, 2 H), 2.40–2.49 (m, 5 H), 4.30 (d, *J* = 0.9 Hz, 2 H), 6.67–6.73 (m, 1 H), 6.96 (t, *J* = 0.9 Hz, 1 H), 7.28 (d, *J* = 7.9 Hz, 2 H), 7.90 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 21.8, 22.1, 24.5, 25.4, 35.9, 125.9, 126.0, 126.2, 128.6, 129.5, 131.0, 133.5, 144.6, 162.9, 193.6.

HRMS: *m*/*z* calcd for $C_{18}H_{19}NO_2$: 281.1416; found: 281.1424.

3q

Acid chlorides **2k** (94 mg, 1.00 mmol) and **2c′** (158 mg, 1.00 mmol) were used according to the general procedure to produce 95 mg (42%) of **3q** as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 4.33 (s, 2 H), 5.56 (d, *J* = 11.4 Hz, 1 H), 6.10 (dd, *J* = 0.9, 17.5 Hz, 1 H), 6.55 (dd, *J* = 11.4, 17.5 Hz, 1 H), 7.03 (s, 1 H), 7.28 (d, *J* = 8.8 Hz, 2 H), 7.90 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 35.8, 121.3, 123.4, 126.6, 128.6, 129.5, 133.4, 144.7, 145.5, 160.9, 193.3.

HRMS: *m*/*z* calcd for $C_{14}H_{13}NO_2$: 227.0946; found: 227.0968.

Acknowledgment

Financial support of the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Studienstiftung des Deutschen Volkes (scholarship for E.M.) is gratefully acknowledged. We also cordially thank BASF AG for generous donation of chemicals.

References

(1) (a) Jacobs, H. M.; Burke, B. A. In *Alkaloids*, Vol. 35; Brossi, A., Ed.; Academic Press: New York, **1989**, 259. (b) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115. (c) Jin, Z. *Nat. Prod. Rep.* **2003**, *20*, 584. (d) *Oxazoles: Synthesis, Reactions, and Spectroscopy, Part A*, Vol. 60; Palmer, D. C., Ed.; Wiley: Hoboken NJ, **2003**.

(2) (a) *Oxazoles: Synthesis, Reactions, and Spectroscopy, Part B*, Vol. 60; Palmer, D. C., Ed.; Wiley: Hoboken NJ, **2004**. (b) Boyd, G. V. In *Science of Synthesis*, Vol. 11; Schaumann, E., Ed.; Georg Thieme Verlag: Stuttgart, **2002**, 383. (c) Hartner, F. W. Jr. In *Comprehensive Heterocyclic Chemistry II*, Vol. 3; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Elsevier: Oxford, **1996**, 261. (d) Maryanoff, B. E. *Chemistry of Heterocyclic Compounds*, Vol. 45; Turchi, I. J., Ed.; Wiley: Chichester, **1986**, 963. (e) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389.

(3) See, for example: (a) Dalvie, D. K.; Kalgutkar, A. S.; Khojasteh-Bakht, S. C.; Obach, R. S.; O'Donnell, J. P. *Chem. Res. Toxicol.* **2002**, *15*, 269. (b) McGovern, S. L.; Caselli, E.; Grigorieff, N.; Shoichet, B. K. *J. Med. Chem.* **2002**, *45*, 1712. (c) Murcia-Soler, M.; Perez-Gimenez, F.; Garcia-March, F. J.; Salabert-Salvador, M. T.; Diaz-Villanueva, W.; Castro-Bleda, M. J.; Villanueva-Pareja, A. *J. Chem. Inf. Comput. Sci.* **2004**, *44*, 1031.

(4) (a) For syntheses of oxazole containing macrocycles and their biological activity, see, for example, ref. 1b. (b) For a recent synthesis, see, for example: Wipf, P.; Graham, T. H. *J. Am. Chem. Soc.* **2004**, *126*, 15346.

(5) (a) Brown, W. K. (John Wyeth & Brothers Ltd.); US Patent 3574228, **1971**; *Chem. Abstr.* **1969**, *71*, 124422. (b) Meguro, K.; Fujita, T. (Takeda Chemical Ind.); US Patent 4596816, **1986**; *Chem Abstr*. **1984**, *100*, 121045.

(6) Wasserman, H. H.; Vinick, F. J. *J. Org. Chem.* **1973**, *38*, 2407.

(7) Dow, R. L. *J. Org. Chem.* **1990**, *55*, 386.

(8) (a) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604. (b) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558. (c) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165. (d) Wipf, P.; Methot, J.-L. *Org. Lett.* **2001**, *3*, 1261.

(9) (a) Wipf, P.; Rahman, L. T.; Rector, S. R. *J. Org. Chem.* **1998**, *63*, 7132. (b) Arcadi, A.; Cacchi, S.; Cascia, L.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2001**, *3*, 2501. (c) Coqueron, P.-Y.; Didier, C.; Ciufolini, M. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1411.
(10) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391.
(11) For reviews, see: (a) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095. (b) Müller, T. J. J. *Chim. Oggi/ Chem. Today* **2007**, *25*, 70. (c) Müller, T. J. J. In *Targets in Heterocyclic Systems: Chemistry and Properties*, Vol. 10; Attanasi, O. A.; Spinelli, D., Eds.; Italian Society of Chemistry: Rome, **2006**, 54. (d) Müller, T. J. J.; D'Souza, D. M. *Pure Appl. Chem.* **2008**, *80*, 609.
(12) Merkul, E.; Müller, T. J. J. *Chem. Commun.* **2006**, 4817.
(13) Wipf, P.; Aoyama, Y.; Benedum, T. E. *Org. Lett.* **2004**, *6*, 3593.
(14) Becker, H. G. O.; Beckert, R.; Domschke, G.; Fanghänel, E.; Habicher, W. D.; Metz, P.; Pavel, D.; Schwetlick, K. *Organikum*, 21st ed.; Wiley-VCH: Weinheim, **2001**.