A New Facile Synthesis of 2-Aroyloxazoles from 2-Lithiooxazoles

Lendon N. PRIDGEN, Susan C. SHILCRAT

Synthetic Chemistry, Chemical Research and Development, Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101, U.S.A.

The synthetic utility of the oxazole heterocycle has been extensively investigated and is continually being advanced. One recent example describes the intermediacy of 5-aminooxazoles in the synthesis of dipeptides[1]. Wasserman et al. have demonstrated how oxazole-based chemistry may lead to many widely diverse structures[2]. Thus, 4,5-diphenyloxazoles may be utilized as masked carboxylic acid derivatives in macrolide synthesis[3]. Also, the usefulness of 4,5-dihydrooxazoles as nucleophile directors[4] has been shown. Because oxazoles are prevalent in many naturally occurring synthetically interesting target molecules, several strategies have been developed to prepare multifunctional oxazole de-

Table 1. *N*-Methyl-*N*-(2-pyridinyl)-carboxamides (**4**) prepared

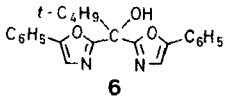
4	Yield[a] [%]	m.p. [°C] or b.p. [°C]/torr	Molecular Formula[b] or Lit. Data [°C]	M.S.[c] (M^+) *m/e* (rel. int., [%])	I.R. (KBr) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[d] δ [ppm]
b	99	b.p. 90–92°/0.2	b.p. 74–80°/0.08[11]	164 (100)	1668 (film)	1.13 (t, 3H); 2.43 (q, 2H); 3.50 (s, 3H); 7.37–8.35 (m, 3H); 8.91 (d, 1H)
c	98	b.p. 136–138°/0.2	b.p. 118–123°/0.08[11]	212 (100)	1655 (film)	3.67 (s, 3H); 6.97–7.97 (m, 8H); 8.78 (d, 1H)
d	91	m.p. 54–55°	$C_{11}H_{16}N_2O$ (192.25)	192 (100)	1635	1.10 (s, 9H); 3.30 (s, 3H); 7.17–7.50 (m, 2H); 7.67–8.03 (m, 1H); 8.47–8.73 (m, 1H)
e	82	b.p. 53–55°/0.4	$C_8H_7F_3N_2O$ (204.15)	204 (100)	1700 (film)	3.55 (s, 3H); 7.50–8.48 (m, 3H); 8.92 (d, 1H)
f	95	b.p. 144–146°/0.2	$C_{14}H_{14}N_2O$ (226.3)	226 (100)	1650 (film)	2.30 (s, 3H); 3.60 (s, 3H); 6.73–7.70 (m, 7H); 8.50 (d, 1H)
g	79	m.p. 81–82°	$C_{14}H_{14}N_2O_2$ (242.3)	242 (100)	1630	3.63 (s, 3H); 3.82 (s, 3H); 6.67–7.73 (m, 7H); 8.50 (d, 1H)
h	85	m.p. 47–48°	$C_{13}H_{11}ClN_2O$ (246.7)	246 (100)	1650	3.58 (s, 3H); 6.75–7.75 (m, 7H); 8.50 (d, 1H)
i	74	m.p. 80–81°	$C_{13}H_{11}FN_2O$ (230.2)	230 (100)	1640	3.58 (s, 3H); 6.73–7.77 (m, 7H); 8.50 (d, 1H)
j	85	m.p. 107–108°	$C_{13}H_{11}N_3O_3$ (257.25)	257 (100)	1655	3.70 (s, 3H); 6.87–7.83 (m, 5H); 8.18 (d, 2H); 8.50 (d, 1H)
k	83	m.p. 101–102°	$C_{14}H_{11}N_3O$ (237.25)	237 (100)	1665	3.67 (s, 3H); 6.85–7.85 (m, 7H); 8.53 (d, 1H)

[a] Yield of isolated product.
[b] The microanalyses were in satisfactory agreement with the calculated values: C ±0.31, H ±0.24, N ±0.28.
[c] Measured on a Finnigan 3600 capillary gas chromatograph using Methane Chemical Ionization Mass Spectrometry.
[d] Measured at 60 MHz using a Varian EM 360L spectrometer.

Table 2. 2-Acyloxazoles (**5**) prepared

Educt	Product	Yield[a] [%]	m.p. [°C]	Molecular Formula[b] or Lit. m.p. [°C]	M.S.[c] (M^+) *m/e* (rel. int. %)	I.R. (KBr) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[d] δ [ppm]
4a	**5a**	61	65–66°	$C_{10}H_7NO_2$ (173.0477)	173.048	1700	7.50–8.30 (m, 6H); 10.20 (s, 1H)
4c	**5c**	13 (18)	133–134°	$C_{16}H_{11}NO_2$ (249.3)	249 (100)	1650	7.15–7.92 (m, 9H); 8.45 (d, 2H)
4f	**5f**	40 (67)	116–117°	$C_{17}H_{13}NO_2$ (263.3)	263 (100)	1645	2.40 (s, 3H); 7.40–8.27 (m, 8H); 8.72 (d, 2H)
4g	**5g**	30 (46)	108–109°	$C_{17}H_{13}NO_3$ (279.3)	279 (98.1)	1642	4.00 (s, 3H); 6.93–8.09 (m, 8H); 8.63 (d, 2H)
4h	**5h**	49 (63)	134–135°	$C_{16}H_{10}ClNO_2$ (283.7)	283 (100)	1657	7.22–8.02 (m, 8H); 8.57 (d, 2H)
4i	**5i**	47 (63)	143–144°	$C_{16}H_{10}FNO_2$ (267.3)	267 (22.8)	1660	6.98–8.05 (m, 8H); 8.42–8.83 (m, 2H)
4j	**5j**	33 (56)	187–188°	$C_{16}N_{10}N_2O_2$ (294.3)	294 (100)	1655	7.73 (s, 1H); 7.87–8.50 (m, 5H); 8.83 (d, 2H); 9.18 (d, 2H)
4k	**5k**	53 (77)	188–189°	$C_{17}H_{10}N_2O_2$ (274.3)	274 (100)	1670	7.65 (s, 1H); 7.77–8.38 (m, 7H); 9.07 (d, 2H)
4d	**6**[e]	22 (41)	126–127°	$C_{23}H_{22}N_2O_3$ (374.16305)	374.164		1.25 (t, 9H); 4.00–4.42 (b, 1H); 7.33–8.00 (m, 12H)

[a] Yield of isolated product, based on **4** submitted to the reaction. Yields in parentheses have been corrected for recovered starting material.
[b] The microanalyses (except for **5a** and **6**) were in satisfactory agreement with the calculated values: C ±0.23, H ±0.32, N ±0.25.
[c,d] see Table 1.
[e] Compound **6**:



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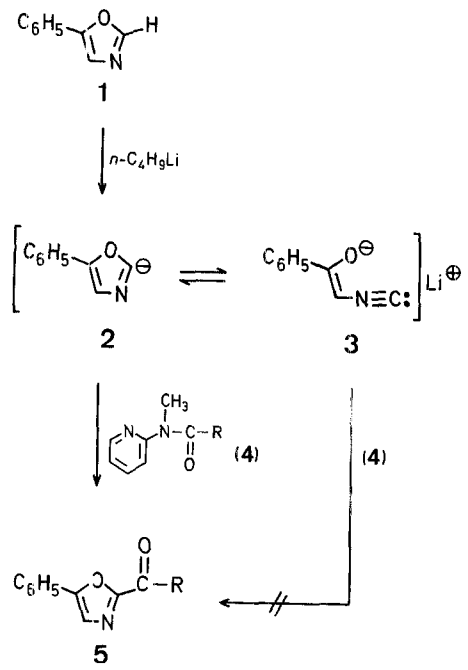
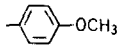
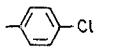
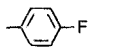
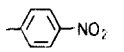
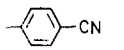
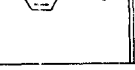
rivatives[5,8]. However, only two successful syntheses of 2-substituted oxazoles from 2-lithiooxazole have been reported to date[9,10]. The electrophile in both cases was an aromatic aldehyde. The difficulty in alkylating or acylating 2-lithiooxazoles has been attributed to the much publicized mobile equilibrium between the open-chain tautomer and the oxazole[9].

N-Methyl-*N*-(2-pyridinyl)-carboxamides (**4**) have been shown to be useful in acylating lithium and Grignard reagents[11,12]. The additional observation[13] that alkoxides are not appreciably reactive with amides **4** prompted us to investigate the feasibility of employing these reagents (Table 1) to acylate anion **2**. Table 2 shows that moderate to good yields of 2-aroyloxazoles (**5**) may be obtained employing aromatic carboxamides (**4f–k**). The reaction generally proceeds even better when the phenyl ring contains an electron-withdrawing substituent (entries **h–k**). A notable exception is the synthesis of the heretofore unreported 2-formyl-5-phenyloxazole **5a** (R = H) in good yield.

Compound **6** (Table 2) was isolated and characterized as the major product formed in the reaction between **2** and **4d**. The formation of this material in substantial quantity illustrated the diminished reactivity of aliphatic amides **4**. In addition, negligible amounts of oxazoles **5** were obtained from amides **4b** and **4e**.



4,5	R	4,5	R
a	H	g	
b	C_2H_5	h	
c		i	
d	t-C_4H_9	j	
e	CF_3	k	
f			

Acylated oxazoles **5** are latent 2-keto and potential amino acid derivatives. This work thus provides a facile entry into this class of compounds.

N-Methyl-N-(2-pyridinyl)-4-cyanobenzamide (4k); Typical Procedure:

To a stirred solution of commercially (Aldrich) available 2-methylaminopyridine (2.16 g, 20.0 mmol) in benzophenone ketyl-dried tetrahydrofuran (25 ml) at −78 °C under nitrogen, is added dropwise a solution of butyllithium (22.1 mmol) in hexanes and stirring is continued at −78 °C for 30 min. The mixture is then allowed to warm to ambient temperature. The reaction is quenched by the addition of water (20 ml) and the mixture is extracted with ether (2 × 25 ml). The combined organic extracts are washed with saturated sodium chloride solution (25 ml), dried with magnesium sulfate, and concentrated. The crude product obtained is purified by flash column chromatography on silica gel using ether/petroleum ether (1/1) as eluent; yield 3.91 g (83%); m.p. 101–102 °C.

2-(4-Cyanobenzoyl)-5-phenyloxazole (5k); Typical Procedure:

To a stirred solution of 5-phenyloxazole[14] (**1**; 0.72 g, 5.0 mmol) in dry tetrahydrofuran (20 ml) + ether (10 ml) at −78 °C under nitrogen is added dropwise a solution of butyllithium (5.5 mmol) in hexanes and stirring at −78 °C is continued for 30 min. Then, a solution of N-methyl-N-(2-pyridinyl)-4-cyanobenzamide (**4k**; 1.78 g, 7.5 mmol) in tetrahydrofuran (7 ml) is added dropwise. After stirring an additional 30 min at −78 °C, the mixture is allowed to warm to room temperature and stirred for 18 h. The mixture is then quenched by the addition of water (20 ml) and extracted with ethyl acetate (3 × 30 ml). The combined organic extracts are washed with 5% hydrochloric acid (25 ml), 5% sodium hydrogen carbonate solution (25 ml), and saturated sodium chloride solution (25 ml), dried with magnesium sulfate, and concentrated. The crude product thus obtained is flash-chromatographed on silica gel using ether/petroleum ether (1/1) as eluent; yield of pure **5k**: 0.72 g (2.63 mmol, 53%); m.p. 188–189 °C. Yield of recovered starting material: 0.29 g (1.24 mmol).

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