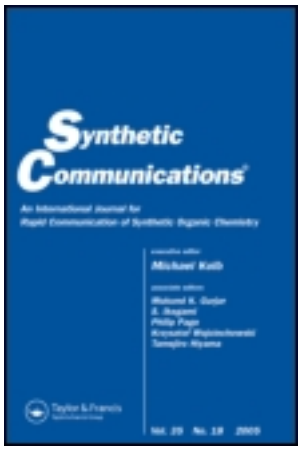


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

PREPARATION OF 2-SUBSTITUTED OXAZOLES

Chennagiri R. Pandit [a], Richard P. Polniaszek [b] & John K. Thottathil [a]

[a] Department of Process Research and Development, Bristol Myers Squibb Pharmaceutical Research Institute, New Brunswick, NJ, 08903, U.S.A.

[b] Department of Process Research and Development, Bristol Myers Squibb Pharmaceutical Research Institute, New Brunswick, NJ, 08903, U.S.A.

Published online: 16 Aug 2006.

To cite this article: Chennagiri R. Pandit , Richard P. Polniaszek & John K. Thottathil (2002): PREPARATION OF 2-SUBSTITUTED OXAZOLES, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:15, 2427-2432

To link to this article: http://dx.doi.org/10.1081/SCC-120006015

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS
Vol. 32, No. 15, pp. 2427–2432, 2002

PREPARATION OF 2-SUBSTITUTED OXAZOLES

Chennagiri R. Pandit, Richard P. Polniaszek,* and John K. Thottathil

Bristol Myers Squibb Pharmaceutical Research Institute, Department of Process Research and Development, New Brunswick, NJ 08903, USA

ABSTRACT

A simple and economical method for 2-substituted oxazole synthesis and its scope are described.

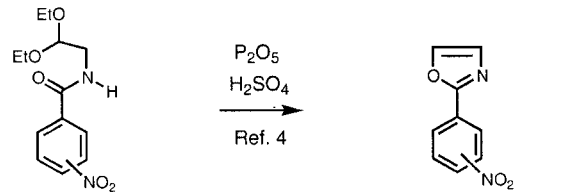
As part of a development program of a cardiovascular drug candidate, it was necessary to prepare large quantities of 2-(4-iodophenyl)oxazole, **3d**. Known methods for the synthesis of 2-substituted-4,5-unsubstituted oxazoles are either indirect,[1] low yielding,[2,4] or require expensive reagents.[3] The simplest way to prepare these heterocycles appeared to be cyclocondensation of the corresponding aroyl amidoacetals, **2**. Cass reported two low yielding examples of this reaction in 1942 (**2j**,**k** to **3a**,**b**).[4] We describe herein improved cyclization conditions as well as a survey of the scope of the reaction.

A variety of aromatic acid chlorides **1** underwent Schotten-Baumann reaction with aminoacetaldehyde dimethyl acetal[5] and the resultant amides **2** were isolated in 75–99% yield by simple extractive workup. The amides thus

*Corresponding author.

DOI: 10.1081/SCC-120006015
0039-7911 (Print); 1532-2432 (Online)

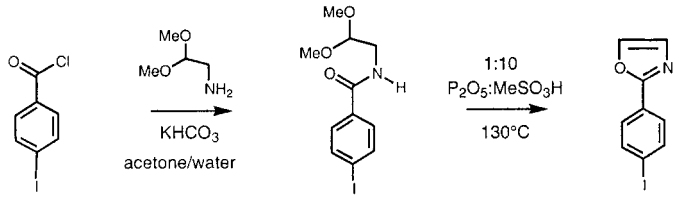
www.dekker.com



2j (ortho isomer)
2k (para isomer)

3a (ortho isomer), 6%
3b (para isomer), 40%

obtained were used in the subsequent step without purification. Preliminary cyclization studies were carried out with the 4-iodophenyl carboxamide **2d** as substrate. Initial screening experiments revealed that catalytic amounts of carboxylic acids in toluene resulted in no reaction, catalytic $MeSO_3H$ in toluene or neat $MeSO_3H$ produced many products, and cyclization in polyphosphoric acid afforded the oxazole **3d** in moderate yield.

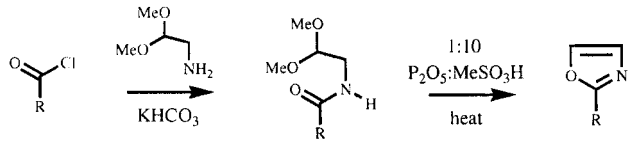


1d **2d** **3d**

The high viscosity of PPA makes this reagent impractical for large scale work and Eaton's reagent,[5,6] a mixture of 1 : 10 P_2O_5 : $MeSO_3H$, is a less viscous, practical alternative with solvent properties similar to PPA. In the event, cyclization of **2d** in neat Eaton's reagent at 130°C for 7.5 h afforded oxazole **3d** which was isolated by precipitation upon dilution of the reaction mixture with water. The oxazole was obtained in 93% unpurified yield with an HPLC purity of 98%. Crystallization afforded analytically pure material in 83% yield from the acid chloride on 200 g scale.

The generality of the method was evaluated by cyclization of a series of amides **2** derived from aromatic and aliphatic acid chlorides. Reactions were run on a 2–4 mmol scale at a concentration of 10 mL/g. Isolation of the oxazoles was effected by dilution onto 10 volumes of water containing 2 g/g of celite, filtration and extractive workup. The methanol liberated during the cyclization was trapped by the mixed anhydride of P_2O_5–$MeSO_3H$ (Eaton's reagent) and formed methyl methanesulfonate as a reaction byproduct. Typically the $MeSO_3Me$ was removed by vacuum drying 48 h at RT and ~1 torr. Purification was achieved by silica gel chromatography.

Table 1.

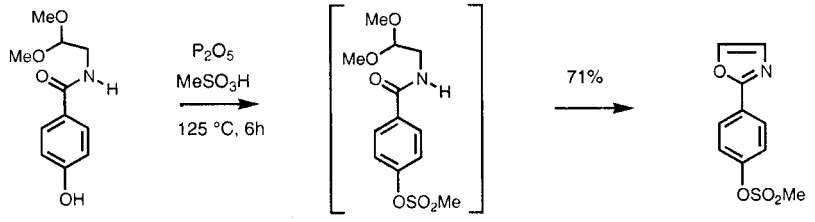


1 **2** **3**

Entry	R	Yield **2** (%)	Cyclization Conditions	Yield **3** (%)
1	**2a**: 2-NO_2–C_6H_4	85[a]	130°C, 1 h	24
2	**2b**: 4-NO_2–C_6H_4	84	130°C, 5 h	73
3	**2c**: 4-Br–C_6H_4	79	150°C, 1.5 h	80
4	**2d**: 4-I–C_6H_4	99	130°C, 7.5 h	83[b]
5	**2e**: 2-CH_3–C_6H_4	92	135°C, 4 h	60
6	**2f**: 3-CH_3-4-BrC_6H_3	95	135°C, 5 h	65
7	**2g**: 4-$CH_3OC_6H_4$	90	135°C, 3 h	0[c]
8	**2h**: 4-HOC_6H_4	75[d]	125°C, 6 h	71, **3i**
9	**2i**: 4-$CH_3O_3SOC_6H_4$	85[e]	125°C, 6 h	72

[a]Prepared from 2-nitrobenzoic acid via the acyl imidazole; [b]200 g scale, crystallized yield; [c]Oxazole not detected, only degradation products; [d]Prepared from 4-acetoxybenzoyl chloride,[7] Isolated as the phenol after hydrolysis of the acetate; [e]Prepared by mesylation of **2j**.

Table 1 lists the results of the cyclocondensation of substituted benzamides classified in descending order into strongly electron deficient (**2a–b)**, mildly electron deficient (**2c–d**), mildly electron rich (**2e–f**), and electron rich (**2g–i**) cases. Eaton's reagent effected cyclization of the *ortho* and *para* nitro benzamides **2a–b** (Entries 1,2). A significant amount of decomposition occurred during cyclization of **2a**. The cyclization is presumably inhibited for steric reasons, and in this case the rate of degradation was competitive with the rate of cyclization. Although the yield of the ortho derivative was modest, the para derivative **2b** cyclized efficiently. The cyclization worked well for substrates possessing mildly electron deficient aromatic rings (Entries 3–4). Although the 2-toluic derivative **2e** cyclized in 60% yield (Entry 5), more electron rich substrates like the 4-methoxy derivative **2g** (Entry 7) of 1-naphthyl (not in Table) suffered extensive degradation under the strongly acidic conditions. The phenol derivative **2h** underwent cyclization to a mesylate ester **3i**.



2h **2i** **3i**

Presumably in this case, the phenol was converted to the mesylate **2i** in situ, which was then deactivated enough to survive the harshly acidic reaction medium. Cyclization of authentic **2i** afforded **3i** in 72% yield (Entry 9), consistent with the intermediacy of **2i** in the cyclization of phenol **2h**.

The method therefore appears to be limited to those substrates which are tolerant of the highly acidic reaction conditions.

In summary, a simple and economical method for the preparation of certain 2-substituted oxazoles amenable to large scale has been achieved which complements existing methods[1–3,8] of oxazole synthesis. The procedure employs inexpensive, commercially available starting materials and reagents.

EXPERIMENTAL

$KHCO_3$ (80.0 g, 0.80 mol) was added to a solution of aminoacetaldehyde dimethyl acetal[5] (82.9 g, 86.0 mL, 0.79 mol) in water (900 mL) and acetone (400 mL) and the resulting solution was cooled in an ice bath to 0°C. A solution of 4-iodobenzoyl chloride (200.0 g, 0.75 mol) in acetone (600 mL) was added dropwise over 1.5 h with stirring. The ice bath was removed and the reaction mixture was stirred at RT for 3 h. One liter of solvent was removed in vacuo and the mixture extracted with EtOAc (4×350 mL). The organic layers were pooled, washed sequentially with saturated $NaHCO_3$ (1×250 mL), H_2O (1×250 mL), dried over anhydrous $MgSO_4$ (50.0 g), filtered and concentrated to afford the amide **2d** as a white solid (246.5 g, 98%, HPLC area percent 99.7, mp 89–90°C). ^{1}H NMR: ($CDCl_3$ 300 MHz, ppm): 7.77 (d, 2H); 7.49 (d, 2H); 6.27 (s, 1H); 4.46 (t, 1H); 3.58 (t, 2H); 3.42 (s, 6H), MS 334 (MH^+).

A solution of the unpurified amide (200.0 g, 0.60 mol) and Eaton's reagent[5,6] (2 L) was stirred and heated under argon, maintaining the internal temperature between 130–134°C. After 7.5 h the reaction mixture

was cooled to RT, poured onto a slurry of ice/water (12.0 L) with vigorous stirring and external cooling (ice water). The resulting suspension was stirred for 2 h, the solid collected, washed with ice cold water (2 L), the filter cake broken and the solid suction dried for 5 days affording a gray powder (151.7 g, 93%, HPLC area percent 98.0). The crude material (151.7 g) was dissolved in acetonitrile (2 L), activated charcoal (15.2 g) was added, stirred at RT for 1 h, filtered through a pad of celite (100 g), the celite pad washed with acetonitrile (2×100 mL), and the filtrate concentrated to approximately 1180 mL. The mixture was warmed until the solid dissolved, boiling water (295 mL) was slowly added, the mixture reheated to effect dissolution, the flask cooled to RT, allowed to stand for 48 h, and then at 4°C. The oxazole was collected, washed with an ice cold acetonitrile/water (4 : 1, 150 mL), and air dried for 16 h, affording **3d** as pale yellow needles (54.8 g, 66%, HPLC area percent 99.7, m.p. 107–109°C). ^{1}H NMR: ($CDCl_3$, 300 MHz, ppm): 7.74–7.82 (m, 4H); 7.70 (s, 1H), 7.22 (s, 1H). Elemental Analysis Calcd for C_9H_6NOl: C, 39.88; H, 2.23; N, 5.17. Found: C, 40.00; H, 2.09; N, 5.14. MS: 272 (MH^+). A second crop from the mother liquor gave an additional 17%, HPLC area percent 98.4.

The ^{1}H NMR spectra of **2a–i** and **3a–f** and **3h–i** were consistent with the assigned structures. The oxazoles **3** displayed the following high resolution mass spectra: **3a**: $C_9H_7N_2O_3^+$, Calcd: 191.0457; Found: 191.0460, m.p. 35–37°C, lit.[4a] 38–39°C; **3b**: $C_9H_7N_2O_3^+$, Calcd: 191.0457; Found: 191.0461, m.p. 159–161°C, lit.[4b] 163.5–164.5°C; **3c**: $C_9H_7NOBr^+$, Calcd: 223.9711; Found: 223.9710, m.p. 84–85.5°C; **3e**: $C_{10}H_{10}N_2O_3^+$ Calcd: 160.0762; Found: 160.0765; oil; **3i**: $C_{10}H_{10}NO_4S^+$, Calcd: 240.0331; Found: 240.0334, m.p. 92–93.5°C. Elemental analysis was obtained for **3f**: Calcd for $C_{10}H_8BrNO$: C, 50.45; H, 3.39; N, 5.88; Br, 33.56. Found: C, 50.10; H, 3.36; N, 5.75; Br, 33.52; m.p. 56°C.

ACKNOWLEDGMENTS

We thank Dr. Kumar Gadamasetti for technical assistance with the preparation of substrates **3f** and **3i**.

REFERENCES

1. Kashima, C.; Arao, H. Synthesis **1989**, 873; Eisenstat, M.A.; Weaver III, J.D. J. Org. Chem. **1993**, *58*, 3387; Meyers, A.l.; Tavares, F. Tet. Lett. **1994**, *35*, 2481.

2. Ferrini, P.G.; Marxer, A. Angew. Chemie Int. Ed. Engl. **1963**, *2*, 99; Maeda, M.; Kojima, M. J. Chem. Soc. Perkin 1 **1977**, 239; Brown, E.V. J. Org. Chem. **1977**, *42*, 3208.
3. Williams, E.L. Tet. Lett. **1992**, *33*, 1033. *The metalation and subsequent Suzuki coupling of oxazole with aryl iodides has been reported.* The preparation of oxazole itself is multi-step. Crowe, E.; Hossner, F.; Hughes, M.J. Tetrahedron **1995**, *51*, 8889; Anderson, B.A.; Becke, L.M.; Booher, R.N.; Flaugh, M.E.; Harn, N.K.; Kress, T.J.; Varie, D.L.; Wepsiec, J.P. J. Org. Chem. **1997**, *62*, 8634.
4. (a) Cass, W.E. J. Am. Chem. Soc. **1942**, *64*, 785; (b) Rosenbaum, J.E.; Cass, W. J. Am. Chem. Soc. **1942**, *64*, 2444.
5. Item of commerce, obtained from Aldrich Chemical Company.
6. Eaton, P.E.; Carlson, G.R.; Le, J.T. J. Org. Chem. **1973**, *38*, 4071.
7. Schoenenberger, H.; Holzhen-Eckardt, J.; Bamann, E. Arzneim Forsch. **1964**, *14*, 324.
8. Review: Turchi, I.J., Ed. Oxazoles. *The Chemistry of Heterocyclic Compounds*, Vol. 45, Wiley: New York, 1986.

Received in the USA August 8, 2001