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A Novel Improved Procedure for the Synthesis of Oxazoles

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Abstract**:** In the present work a novel improved and convenient procedure for the synthesis of oxazoles has been developed. Acetamide, instead of ammonium acetate, was used to react with phenacyl benzoates in boiling xylene in the presence of BF_3/Et_2O as the catalyst. According to this new synthetic route, nine oxazole compounds were readily prepared as single products in reasonably high yields. On the basis of the experimental results, a plausible mechanism of this reaction is proposed. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

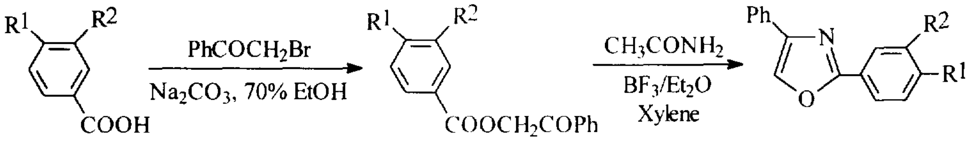
It is well known that oxazole nucleus is rarely found in nature. During the past three decades, some alkaloids have been proved to be relatively simple substituted oxazoles. Several oxazole natural products have been isolated from plants. Oxazoles have been used in a great number of syntheses.[1-5] In addition, oxazoles, especially diaryl and arylstryryl ones, are quite useful as antibacterial, antimicrobial, antiviral and analgesic drugs.[6-8]

Although there are many different ways to synthesise oxazoles,[9,10] unfortunately, most of them suffer from lack of generality due to various reasons, such as rare availability of starting materials, rigorous reaction conditions, lengthy and complicated procedures, *etc.* The formation and reactions of substituted oxazoles from α-acyloxy ketones have been studied by several authors,[11-14] however, all the procedures give rise concomitantly to a by-product, imidazole. Therefore, the yields are not satisfactorily high, only about 40-70%.

In this paper, we describe a novel improved and feasible synthetic method for the synthesis of oxazole. Acetamide, instead of ammonium acetate, was used as the nitrogen source to react with phenacyl benzoates in boiling xylene in the presence of BF_3/Et_2O as the catalyst. By means of this improved procedure, nine oxazole compounds were readily obtained as single products in high yields. In addition, a plausible mechanism of this reaction is proposed based on our experimental results and observations.

RESULTS AND DISCUSSION

In order to synthesise a natural product, it is essential for us to employ a convenient way to synthesise oxazoles since they are the key starting materials. At the first stage of our investigations, we tried to utilise H. Bredereck's synthetic method reported in 1953,[15] unfortunately, we could not repeat their results under similar conditions. Afterwards, in search of an alternative and feasible synthetic pathway to synthesise oxazoles, we contrived a new improved and quite convenient procedure shown as follows (Scheme 1):

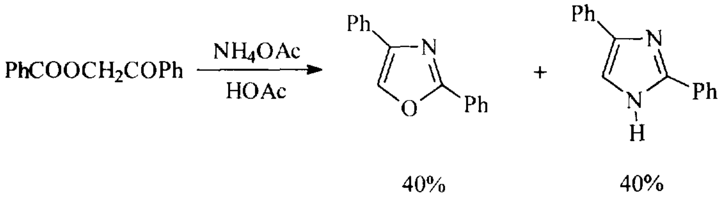


1 **2** **3**

	a	b	c	d	e	f	g	h	i
R1	H	CH_3	CH_3O	CH_3O	OCH_2O	BnO	OH	Cl	Cl
R2	H	H	H	CH_3O		CH_3O	CH_3O	H	Cl

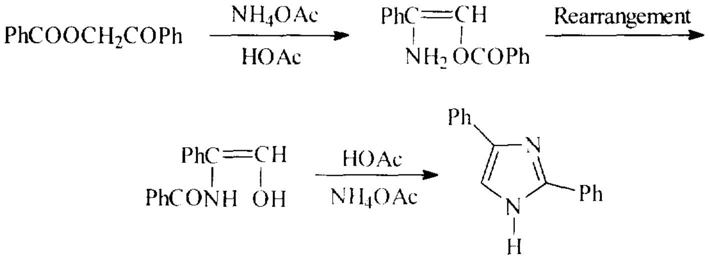
Scheme 1

We know that phenacyl bromide has the advantage of being readily made, hence, phenacyl acetate could be prepared quite conveniently, too.[16] Therefore, **2a** was allowed to react with ammonium acetate in boiling acetic acid to afford a mixture of 2,4-diphenyloxazole and 2,4-diphenylimidazole, from which the two compounds were separated with each a yield of around 40% (Scheme 2).



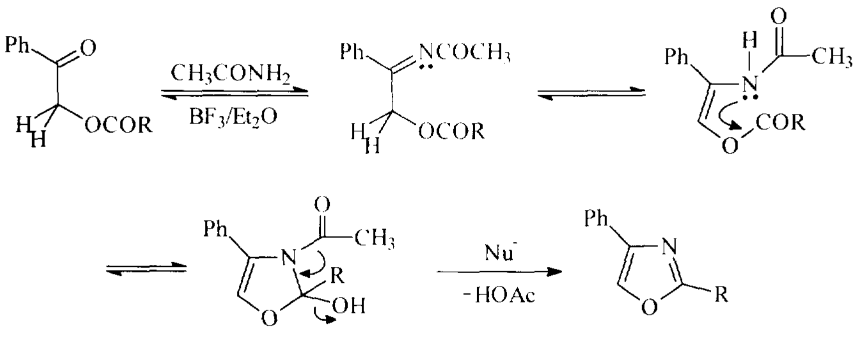
Scheme 2

Similar results were also obtained with the use of other esters, thus, we think that the interaction of such ketone esters **2** with ammonium acetates forms the desired product oxazoles always together with the corresponding imidazoles, which results in the yields quite low. Hence, it is reasonable to believe that the by-product imidazoles are formed due to using ammonium acetate (Scheme 3).[14]



Scheme 3

In order to inhibit the reaction from the undesired rearrangement, acetamide instead of ammonium acetate was used to react with phenacyl benzoates **2** to get better yields of oxazoles under similar conditions. According to scheme 3, if acetamide is used, the rearrangement cannot occur, hence, the by-product, imidazole, will not be yielded. However, after many trial experiments were carried out, it was found that the esters **2** could not be converted into oxazoles under the same reaction condition. When other protonic acids, such as sulphuric acid, phosphorus pentachloride, thionyl chloride and polyphosphoric acid instead of acetic acid were used, either the reaction speed was very slow or nothing occurred at all. After having finished trying these protonic acids, finally, we found and believed that BF_3/Et_2O as the catalyst could turn ketone into amine.



Scheme 4

If 5 mol% BF_3 was used as the catalyst, the esters **2** could be converted smoothly to oxazole **3** in boiling xylene in high yields without any by-products. It can be seen from the experimental results that the yields are favoured with those benzoates having electron-donating substituents in the benzene rings. In the mean time, the influence of OH group on this reaction was investigated. It was found that the yield with OH substitution was similar to those of other substitution groups, but halo- groups made yields a little lower. Based on these experimental results and observations described above, a plausible mechanism of this formation is proposed as above (Scheme 4).

EXPERIMENTAL

Reagents and solvents were purified in the usual way. Melting points were determined on a Yanaco MP-500 apparatus and were not corrected. Infrared (IR) spectra were recorded on a Vicolet Magna 750 IR spectrophotometer. ^{1}H NMR were recorded on a BRUKER ARX 400 instrument, and chemical shifts are expressed in δ-values relative to TMS. Mass spectral analyses were carried out on a VG-ZAB-HS mass spectrometer.

Preparation of Esters 2

To a suspension of compound **1** (0.052 mol) in 150 ml 70% ethanol-water, Na_2CO_3 (0.048 mol) was added. The solution was stirred until the solid was dissolved completely, then phenacyl bromide (0.05 mol) and 50 ml 95% ethanol were added, and the solution was refluxed for 1.5 hours. The solution was cooled rapidly under the tap with constant shaking. The crystals were filtered, washed with 70% ethanol and water. Recrystallisation from 70% ethanol gave a white, needle solid.

2a: (yield, 96.1%), mp: 117-8°C; **IR** (ν, cm^{-1}): 2990, 1710, 1600, 1280, 755, 710; ^{1}**H NMR** (δ, ppm): 7.26-7.99 (8H, m, Ar-H), 5.53 (2H, s, $-OCH_2CO-$); **MS** (EI, m/e): 240 ($M^{\bullet+}$), 121 $(M–PhCOCH_2)^+$, 105 ($PhCO^+$, 100%); **Anal.** Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.95; H, 5.05.

2b: (97.2%), mp: 89-90°C; **IR** (ν, cm^{-1}): 2995, 1705, 1600, 815, 755, 720, 700; ^{1}**H NMR** (δ, ppm): 7.70-8.01 (4H, m, Ar-H), 7.21-7.50 (5H, m, Ar-H), 5.53 (2H, s, $-OCH_2CO$), 2.43 (3H, s, $-CH_3$); **MS** (EI, m/e): 254 ($M^{\bullet+}$), 135 $(M–PhCOCH_2)^+$, 105 ($PhCO^+$, 100%); **Anal.** Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.50; H, 5.53.

2c: (96.7%), mp: 126-8°C; **IR** (ν, cm^{-1}): 2990, 1700, 1600, 835, 750; ^{1}**H NMR** (δ, ppm): 7.80-8.10 (4H, m, Ar-H), 6.80-7.40 (5H, m, Ar-H), 5.54 (2H, s, $-OCH_2CO$), 3.96 (3H, s, $-OCH_3$); **MS** (EI, m/e): 270 ($M^{\bullet+}$), 151 $(M–PhCOCH_2)^+$, 105 ($PhCO^+$, 100%); **Anal.** Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.03; H, 5.24.

2d: (98.3%), mp: 127-8°C; **IR** (ν, cm^{-1}): 2995, 1695, 1600, 1440, 1250, 750, 680; ^{1}**H NMR** (δ, ppm): 6.91-8.03 (8H, m, Ar-H), 5.53 (2H, s, $-CH_2-$), 4.00 (3H, s, $-OCH_3$), 3.95 (3H, s, $-OCH_3$); **MS** (EI, m/e): 300 ($M^{\bullet+}$), 181 $(M–PhCOCH_2)^+$, 105 ($PhCO^+$, 100%); **Anal.** Calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 68.05; H, 5.30.

2e: (97.2%), mp: 125-6°C; **IR** (ν, cm^{-1}): 2995, 1710, 1695, 1600, 1440, 1250, 750, 680; ^{1}**H NMR** (δ, ppm): 6.89-8.05 (8H, m, Ar-H), 6.05 (2H, s, $-OCH_2O-$), 5.55 (2H, s, $-CH_2-$), **MS** (EI, m/e): 284 ($M^{\bullet+}$), 149 $(M–PhCOCH_2)^+$, 105 ($PhCO^+$, 100%); **Anal.** Calcd. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.25. Found: C, 67.51; H, 4.20.

2f: (98.7%), mp: 139-140°C; **IR** (ν, cm^{-1}): 2950, 1700, 1595, 1270, 1210, 750, 695; **^{1}H NMR** (δ, ppm): 6.91-7.97 (8H, m, Ar-H), 5.54 (2H, s, $-OCH_2CO-$), 5.23 (2H, s, $-OCH_2-$), 3.94 (3H, s, $-OCH_3$); **MS** (EI, m/e): 376 ($M^{\bullet +}$), 285 $(M-C_7H_7)^+$, 105 ($PhCO^+$), 91 ($C_7H_7^+$, 100%); **Anal.** Calcd. for $C_{23}H_{20}O_5$: C, 73.39; H, 5.36. Found: C, 73.31; H, 5.42.

2g: (89.7%), mp: 113-5°C; **IR** (ν, cm^{-1}): 3600, 3520, 2960, 1690, 1640, 1590, 1290, 1210, 760, 690; **^{1}H NMR** (δ, ppm): 6.95-7.98 (8H, m, Ar-H), 6.24 (1H, br, -OH), 5.56 (2H, s, $-CH_2-$), 3.93 (3H, s, $-OCH_3$); **MS** (EI, m/e): 286 ($M^{\bullet +}$), 151 $[(M-OCH_2COPh)^+$, 100%]; **Anal.** Calcd. for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 67.15; H, 4.97.

2h: (92.1%), mp: 81-2°C; **IR** (ν, cm^{-1}): 2995, 1700, 1595, 820, 755, 720, 690; **^{1}H NMR** (δ, ppm): 7.75-8.03 (4H, m, Ar-H), 7.33-7.51 (5H, m, Ar-H), 5.54 (2H, s, $-OCH_2CO$); **MS** (EI, m/e): 274 ($M^{\bullet +}$), 155 $(M-PhCOCH_2)^+$, 105 ($PhCO^+$, 100%); **Anal.** Calcd. for $C_{15}H_{11}ClO_3$: C, 65.59; H, 4.04; Cl, 12.91. Found: C, 65.63; H, 4.01; Cl, 12.85.

2i: (91.2%), mp: 98-9°C; **IR** (ν, cm^{-1}): 2985, 1695, 1590, 830, 755, 720, 685; **^{1}H NMR** (δ, ppm): 7.30-8.21 (8H, m, Ar-H), 5.53 (2H, s, $-OCH_2CO$); **MS** (EI, m/e): 308 ($M^{\bullet +}$), 189 $(M-PhCOCH_2)^+$, 105 ($PhCO^+$, 100%); **Anal.** Calcd. for $C_{15}H_{10}Cl_2O_3$: C, 58.28; H, 3.26; Cl, 22.94. Found: C, 58.01; H, 3.21; Cl, 23.01.

Preparation of Oxazoles **3**

After 0.05 mol acetamide was added to a suspension of 0.01 mol ester **2** in 100 ml xylene, 47% BF_3/Et_2O (0.7 ml) was added dropwise. The solution was refluxed for over 20 hours. After the ester **2** could not be detected by TLC, the solution was quenched with cold water (50 ml), and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with bromine, dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo to afford the crude product as a red solid. Recrystallisation from 95% ethanol gave a white, needle solid.

3a: (85.1%), mp: 105-6°C; **IR** (ν, cm^{-1}): 1600, 1560, 1485, 1080, 935, 780, 750, 715, 696; **^{1}H NMR** (δ, ppm): 7.95 (1H, s, Oxz-H), 7.35-8.19 (10H, m, Ar-H); **MS** (EI, m/e): 221 ($M^{\bullet +}$, 100%), 193 $(M-CO)^+$; **Anal.** Calcd. for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.36; H, 4.91; N, 6.29.

3b: (81.4%), mp: 116-7°C; **IR** (ν, cm^{-1}): 1605, 1490, 1270, 1075, 935, 820, 755, 728, 695; **^{1}H NMR** (δ, ppm): 7.94 (1H, s, Oxz-H), 7.82-8.02 (4H, m, Ar-H), 7.44-7.25 (5H, m, Ar-H), 2.41 (3H, s, $-CH_3$); **MS** (EI, m/e): 235 ($M^{\bullet +}$, 100%), 207 $(M-CO)^+$; **Anal.** Calcd. for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.64; H, 5.53; N, 5.89.

3c: (86.7%), mp: 101-2°C; **IR** (ν, cm^{-1}): 1605, 1490, 1250, 1010, 930, 835, 730, 685; **^{1}H NMR** (δ, ppm): 7.92 (1H, s, Oxz-H), 7.81-8.08 (4H, m, Ar-H), 6.78-7.45 (5H, m, Ar-H), 3.87 (3H, s, $-OCH_3$); **MS** (EI, m/e): 251 ($M^{\bullet +}$, 100%), 223 $(M-CO)^+$, 208 $(M-COMe)^+$; **Anal.** Calcd. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.32; H, 5.13; N, 5.45.

3d: (89.2%), mp: 123-4°C; **IR** (ν, cm^{-1}): 1605, 1510, 1250, 1020, 945, 850, 735, 695; **^{1}H NMR** (δ, ppm): 7.93 (1H, s, Oxz-H), 7.69-7.83 (3H, m, Ar-H), 6.94-7.66 (5H, m, Ar-H), 4.01 (3H, s, $-OCH_3$), 3.95 (3H, s, $-OCH_3$); **MS** (EI, m/e): 281 ($M^{\bullet +}$, 100%), 253 $(M-CO)^+$, 238 $(M-CO-Me)^+$; **Anal.** Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.34; H, 5.45; N, 4.84.

3e: (84.2%), mp: 98-9°C; **IR** (ν, cm^{-1}): 1600, 1480, 1250, 1050, 940, 730, 696; **^{1}H NMR** (δ, ppm): 7.99 (1H, s, Oxz-H), 6.96-7.89 (8H, m, Ar-H), 6.10 (2H, s, $-OCH_2O-$); **MS** (EI, m/e): 265 ($M^{\bullet +}$,100%), 237 $(M-CO)^+$; **Anal.** Calcd. for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N, 5.28. Found: C, 72.41; H, 4.12; N, 5.29.

3f: (81.2%), mp: 114-6°C; **IR** (ν, cm^{-1}): 1600, 1510, 1280, 1000, 960, 750, 695; **^{1}H NMR** (δ, ppm): 7.91 (1H, s, Oxz-H), 6.94-7.83 (13H, m, Ar-H), 5.22 (2H, s, -OCH$_2$), 4.00 (3H, s, -OCH$_3$); **MS** (EI, m/e): 357 (M$^+$), 266 (M–C$_7$H$_7$)$^+$, 238 M–C$_7$H$_7$–CO)$^+$, 91 (C$_7$H$_7$$^+$, 100%); **Anal.** Calcd. for C$_{23}$H$_{19}$NO$_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.03; H, 5.23; N, 4.04.

3g: (80.6%), mp: 124-6°C; **IR** (ν, cm^{-1}): 3600, 3400, 1600, 1510, 1420, 1280, 1130, 795, 730, 690; **^{1}H NMR** (δ, ppm): 7.91 (1H, s, Oxz-H), 6.99-7.83 (8H, m, Ar-H), 6.20 (1H, br, -OH), 3.98 (3H, s, -OCH$_3$); **MS** (EI, m/e): 267(M$^{\bullet+}$,100%), 239 (M–CO)$^+$, 224 (M–COMe)$^+$; **Anal.** Calcd. for C$_{16}$H$_{13}$NO$_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.88; H, 4.91; N, 5.20.

3h: (78.1%), mp: 145-6°C; **IR** (ν, cm^{-1}): 1600, 1480, 1080, 900, 835, 760, 732, 686; **^{1}H NMR** (δ, ppm): 7.97 (1H, s, Oxz-H), 7.81-8.08 (4H, m, Ar-H), 7.35-7.48 (5H, m, Ar-H); **MS** (EI, m/e): 255 (M$^{\bullet+}$,100%), 227 (M–CO)$^+$, 192 (M–CO–Cl)$^+$; **Anal.** Calcd. for C$_{15}$H$_{10}$ClNO: C, 70.46; H, 3.94; N, 5.48; Cl, 13.86. Found: C, 70.27; H, 3.86; N, 5.39; Cl, 13.71.

3i: (75.2%), mp: 114-5°C; **IR** (ν, cm^{-1}): 1545, 1460, 1080, 900, 840, 760, 726, 697; **^{1}H NMR** (δ, ppm): 7.99 (1H, s, Oxz-H), 7.36-8.23 (8H, m, Ar-H); **MS** (EI, m/e): 289 (M$^{\bullet+}$, 100%), 261 (M–CO)$^+$, 226 (M–CO–Cl)$^+$, 191 (M–CO–2Cl)$^+$; **Anal.** Calcd. for C$_{15}$H$_9$Cl$_2$NO: C, 62.09; H, 3.13; N, 4.83; Cl, 24.44. Found: C, 62.29; H, 3.09; N, 4.79; Cl, 24.38.

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