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Unexpected thermal rearrangement of *N*-alkoxycarbonyl imidazole acryl azides to imidazo[1,5-*c*]pyrimidinone or imidazo[4,5-*c*]pyridinone

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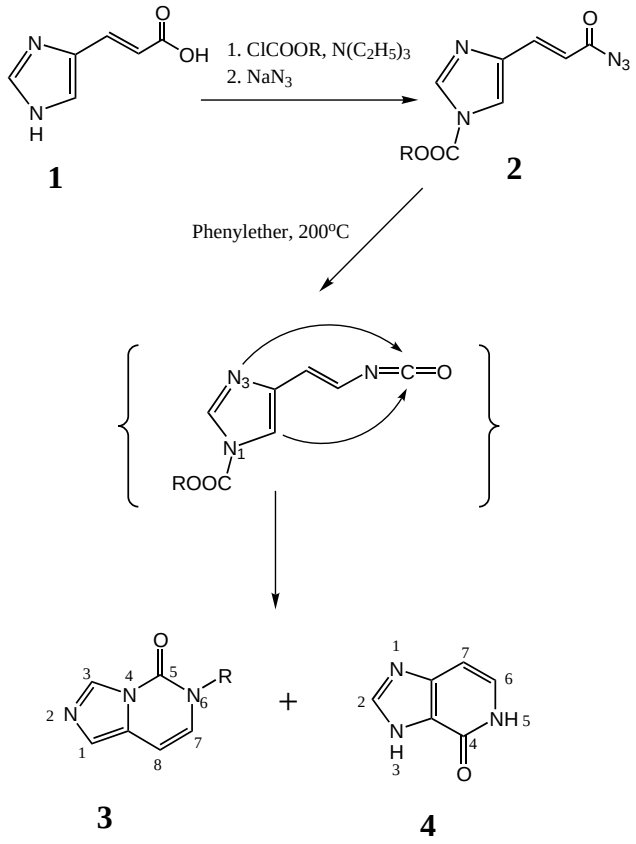
Abstract—Rearrangement of alkoxycarbonyl imidazole acryl azides in phenyl ether at 200°C yields imidazo[1,5-*c*]pyrimidinone or imidazo[4,5-*c*]pyridinone derivatives, depending on the size of the alkoxy substituent.

Curtius rearrangement of acyl azides, yielding a reactive isocyanate intermediate, is an important reaction used in the preparation of amines, isocyanates, and amides. We are particularly interested in the rearrangement of imidazole acryl azide since it may lead to fused-ring heterocycles including imidazo[4,5-*c*]pyridine (3-deazapurine) derivatives, which have shown strong antiviral activity and have been incorporated into nucleic acids for structural studies.[1] It has been reported that the thermal rearrangement of pyrrole, furan, and thiophene acryl azides leads to the formation of fused-ring pyridones.[2] It was proposed that the side chain acryl azide first rearranged into an isocyanate, followed by intramolecular aromatic substitution by the electrophilic isocyanate carbon. Following the same reaction pattern, a rearrangement of 4-imidazole acryl azide would yield imidazo[4,5-*c*]pyridin-4(5*H*)-one, which can be converted to compounds such as 3-deazapurine that has traditionally been synthesized using lengthy procedures.[1,3] This approach has not been followed to our knowledge. One reason for this may be that the imidazole ring is less electron-rich than furan or pyrrole rings since the second nitrogen atom in imidazole serves as a pyridine-like electron withdrawing nitrogen. However, it has been known that imidazole reacts with isocyanate under mild conditions to form *C*-substituted products, imidazole-1-carboxamides, at temperatures reached in boiling nitrobenzene (>200°C).[4] In light of this, we report the synthesis and thermal rearrangement of 3-(1-alkoxycarbonylimidazol-



Scheme 1.

Keywords: rearrangement; imidazole; acryl azide; imidazopyridinone; imidazopyrimidinone.

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4-yl)acryl azides that yield either an alkyl imidazo[1,5-*c*]pyrimidinone or an imidazo[4,5-*c*]pyridinone, depending on the size of the alkyl substituent.

Starting with commercially available urocanic acid (**1**), the active anhydride was formed with alkyl chloroformate in the presence of triethylamine in cold acetone. Without isolation, this was allowed to react with sodium azide in one-pot[5] to form the desired azides **2a**–**e**, 3-(1-*N*-alkoxycarbonylimidazol-4-yl)acryl azides (Scheme 1). The isolated yields were all greater than 48% (Table 1). The structure of the imidazole acryl azides was established through X-ray crystallography of **2a**, which places the methoxycarbonyl group at N-3 nitrogen, as shown in Fig. 1.

Thermolyses of **2a**–**e** were carried out in dry phenyl ether at 200°C under argon protection.[6] Both the argon protective atmosphere and moisture exclusion were necessary for the successful rearrangements. TLC showed that a main product was usually accompanied by some minor by-products. The main thermolysis product of each acryl azide was purified by column chromatography and characterized. The thermolysis of **2a** or **2b** yielded 6-methyl or 6-ethyl imidazo[1,5-*c*]pyrimidin-5(6*H*)-one, **3a** or **3b**, respectively. The structure of **3b** was assigned by X-ray crystallography, as shown in Fig. 2.

Table 1. Synthesis and rearrangement of substituted azides

Entry		Yield (%)		
		2	**3**	**4**
a	R = CH_3	64	46	–[a]
b	R = CH_2CH_3	48	41	–[a]
c	R = $CH_3CH_2CH_3$	55	–[b]	38
d	R = CH $(CH_3)_2$	51	–[b]	31
e	R = C_6H_5	49	–[b]	10

[a] Compound **4** was detected with both TLC and GC–MS as a trace product in the thermolysis of **2a** and **2b**.

[b] A trace amount of a product matching the mass of **3c**, **3d**, and **3e** was detected with GC–MS for the thermolysis of **2c**, **2d**, and **2e**, respectively.

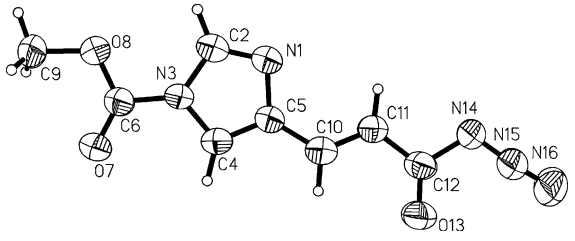

Figure 1. X-Ray crystal structure of 3-(1-*N*-methoxycarbonylimidazol-4-yl)acryl azide (**2a**). Compound **2a** crystallizes in the triclinic system, space group $P\bar{1}$ (no. 2), with a = 3.994(4), b = 11.731(13), c = 12.246(14) Å; α = 61.6(6), β = 87.5(9), γ = 90.0(8)°; Z = 2. Final R_1 for the slightly non-planar molecule was 0.0518 for 867 data for which $I>2\sigma(I)$.

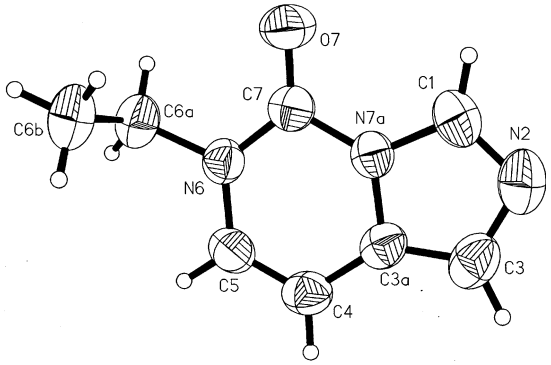

Figure 2. X-Ray crystal structure of 6-ethyl imidazo[1,5-*c*]pyrimidin-5-one (**3b**). Compound **3b** crystallizes in the monoclinic system, space group $P2_1/c$ (no. 14), with a = 7.663(2), b = 9.389(3), c = 11.176(3) Å; β = 92.70(2)°; Z = 4. Final R_1 was 0.0396 for 956 data for which $I>2\sigma(I)$. No disordered atoms were encountered, and all bond lengths and angles are within normal ranges.

The formation of the alkyl imidazo[1,5-*c*]pyrimidin-5(6*H*)-one can be accounted for by ring closure between the imidazole nitrogen (N-3 in Scheme 1) and the isocyanate carbon (Scheme 1). The isocyanate is formed through the rearrangement of the azide. However, the mechanism for the migration of the methyl or ethyl group from the carboxylate group to the isocyanate nitrogen is not clear. Among the minor products, imidazo[4,5-*c*]pyridin-4(5*H*)-one (**4**), a known compound,[7] was present on GC–MS with a m/z of 135 and matching retention time with the main product from the rearrangement of **2c**–**e**.

Thermal rearrangement of azides **2c**–**e** did not yield the alkyl imidazo[1,5-*c*]pyrimidin-5(6*H*)-ones as for the rearrangement of **2a** and **2b**. Instead, the major product isolated from the rearrangement reaction of **2c** was imidazo[4,5-*c*]pyridin-4(5*H*)-one (**4**). The formation of this product is similar to the formation of fused-ring pyridones from the thermal rearrangement of pyrrole, furan, and thiophene acryl azides.[2] In short, the azide first rearranged to become isocyanate, followed by aromatic substitution of the isocyanate carbon on the imidazole ring C-4 carbon (Scheme 1). In this reaction, the minor product has a mass of 177 (GC–MS). Too little of it was formed to be isolated for further characterization. Based on its mass, it would be consistent with 6-propyl imidazo[1,5-*c*] pyrimidin-5(6*H*)-one, the normal rearrangement product as for **2a** and **2b**. Thermal rearrangement of **2d** also resulted in **4** with 31% isolated yield. The rearrangement for **2e** resulted in a rather complex mixture of products as shown by TLC. The main isolated product was again **4**, but only in 10% yield. Among the rearrangement products from **2d** and **2e**, **3d** and **3e** were detected by GC–MS, but too little of it was formed for further characterization.

It seems that both the alkyl substituted imidazo[1,5-*c*]pyrimidin-5(6*H*)-one and the imidazo[4,5-*c*]pyridin-4(5*H*)-one are formed for the thermolysis of 3-(1-alkoxycarbonylimidazol-4-yl)acryl azides **2a**–**e**. If the alkyl group is methyl or ethyl, the alkyl imi-

dazo[1,5-*c*]pyrimidin-5(6*H*)-one is the main product; if the alkyl substituent is bulkier (propyl, isopropyl and phenyl), the rearrangement results in imidazo[4,5-*c*]pyridin-4(5*H*)-one. Both classes of compounds are fused-ring heterocycles that have potential use as antibiotics or as probes for studying nucleic acid structure and dynamics after incorporation into DNA. After optimization, this method may be useful for preparation of these types of compounds with relatively short reaction steps compared to published procedures.[1,3] Further studies are necessary to optimize the conditions to improve the product yields, and to fully understand the rearrangement mechanism.

Acknowledgements

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5. **Procedure for the one-pot preparation of acryl azides 2a–e from urocanic acid**: In a 100 mL flask, a mixture of 10 mmol of urocanic acid and 1.5 mL (10 mmol) of triethylamine in 50 mL of acetone was cooled to 0–5°C with an ice-bath. Then 1.0 mL of alkyl chloroformate (methyl, ethyl, propyl, isopropyl, and phenyl) in 15 mL of acetone was added dropwise in 20 min and the mixture was stirred at 0°C for 1 h in order for the formation of the anhydride to complete. After this, 0.75 g (11 mmol) of NaN_3 in 10 mL of water was added in one portion and the stirring was continued for 3 h at room temperature, until the anhydride disappeared as monitored by TLC. After evaporation of the solvent, the residue was taken into CH_2Cl_2 (50 mL), washed with saturated $NaHCO_3$ and dried over Na_2SO_4. After evaporation of the solvent, the residue was recrystallized from acetone/water. 3-(1-*N*-Ethoxylcarbonylimidazol-4-yl) acryl azide **2a**: mp 124°C (decomp.), IR (KBr): 2151 cm^{-1} for azide, 1757 and 1675 cm^{-1} for the two carbonyls. ^1H NMR ($CDCl_3$): δ 8.18 (s, 1H), 7.62 (s, 1H), 7.58 (d, 1H), 6.66 (d, 1H), 4.08 (s, 3H). Compound **2b**: mp 116°C (decomp.); IR(KBr) 2140 (N_3), 1760, 1757 cm^{-1} for the two carbonyl groups; ^1H NMR ($CDCl_3$): δ 8.22 (s, 1H), 7.64 (s, 1H), 7.58 (d, 1H, $J=16$ Hz), 6.72 (d, 1H, $J=16$ Hz), 4.50 (q, 2H), 1.42 (t, 3H); M^+ m/z 235. Compound **2c**: mp 96°C (decomp.); IR (KBr): 2154 cm^{-1} for azide, 1760 and 1678 cm^{-1} for the two carbonyls. ^1H NMR ($CDCl_3$): δ 8.17 (s, 1H), 7.62 (s, 1H), 7.60 (d, 1H), 6.69 (d, 1H), 4.43 (t, 2H), 1.86 (m, 2H), 1.06 (t, 3H). Compound **2d**: mp 112°C (decomp.); IR (KBr): 2152 cm^{-1} for azide, 1746 and 1680 cm^{-1} for the two carbonyls. ^1H NMR ($CDCl_3$): δ 8.15 (s, 1H), 7.62 (s, 1H), 7.58 (d, 1H), 6.66 (d, 1H), 5.25 (m, 1H), 1.46 (d, 6H). Compound **2e**: mp 84°C (decomp.); IR (KBr): 2154, 1773, 1676 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.34 (s, 1H), 7.78 (s, 1H), 7.61–7.67 (d, 1H), 7.47–7.23 (m, 5H), 6.69–6.75 (d, 1H).
6. **General procedure for the thermal rearrangement of azides 2a–e**: Azide **2b** (200 mg) in 25 mL dry phenyl ether was heated at 200°C for 1 h under argon gas protection. After removal of the solvent phenyl ether with vacuum distillation, the residue was purified by silica gel column chromatography eluting with ethyl acetate/hexane (4:1). After evaporation of the solvents, product **3b** (82 mg, 41%) was obtained and recrystallized from methanol/water. Compound **3a**: mp 116–117°C. IR (KBr): 1702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.41 (s, 1H), 7.20 (s, 1H), 6.54 (d, 1H), 6.43 (d, 1H), 3.54 (s, 3H); ^{13}C NMR ($CDCl_3$): 146, 131.3, 129.7, 124.5, 122.8, 97.8, 36.5; MS: M^+ m/s 149. Compound **3b**: mp 119°C; IR (KBr): 1700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.42 (s, 1H), 7.20 (s, 1H), 6.58 (d, 1H, $J=7.0$ Hz), 6.45 (d, 1H, $J=7.0$ Hz), 3.98 (q, 2H), 1.42 (t, 3H). ^{13}C NMR ($CDCl_3$): δ 141.0, 131.7, 129.1, 126.4, 123.1, 98.8, 44.4, 14.7; MS: M^+ m/s 163. Compound **4**: mp >300°C (lit.[7]); MS: M^+ m/s 135; ^1H NMR (DMSO-d_6): δ 8.45 (s, 1H), 6.63 (d, 1H), 6.48 (d, 1H).
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