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A Simple Synthesis of New Push-Pull Substituted Imidazoles by Chemoselective Nucleophilic Attack of α-Cyano Epoxides.

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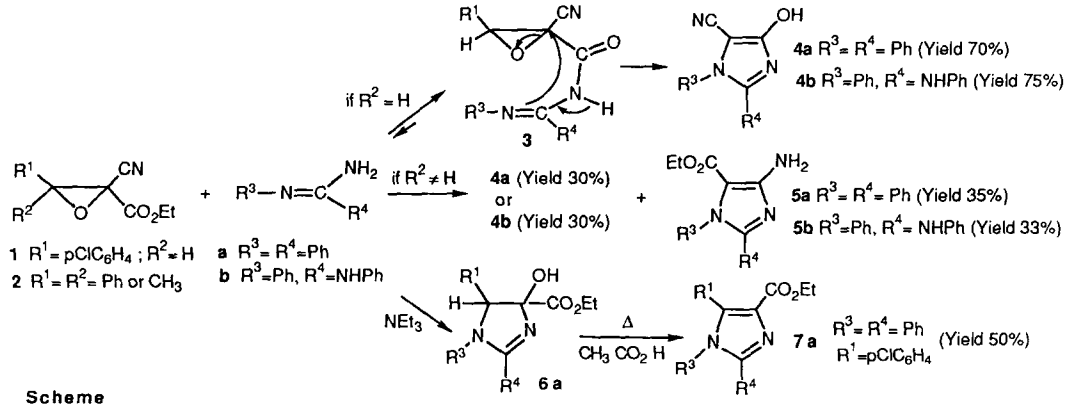
Abstract : A chemoselective reaction of amidines or guanidines with α- cyano epoxides leads to new 4-amino-5-carbethoxy or 4-hydroxy-5-cyano or 4-carbethoxy-5-aryl- imidazoles depending on the steric hindrance of the epoxides and on the reaction medium.

We have already described a chemoselective nucleophilic attack of a cyano group followed by ring opening on gem dicyano epoxides : enaminonitrile dithioles[1] or enaminonitrile imidazoles[2] were obtained. The synthetic interest of such a chemoselective reaction prompted us to extend its scope to the synthesis of poorly represented imidazoles which are nevertheless important precursors of purines (4-amino-5-carbethoxy-imidazoles)[3-6] or interesting insecticides (4-hydroxy-5-cyano-imidazoles).[7] In this paper we will describe the synthesis of such compounds starting from α - functionalized oxiranes **1** or **2**.

It is known that the reactivity of functional group α to an epoxide ring is linked to the steric hindrance of the substituents on the β carbon.[8-11] We observed that the amidine **a** or the guanidine **b** reacted on either the nitrile or the ester group of the epoxide **1** or **2** depending on the substitution of the epoxide (Scheme) :

- Trisubstituted epoxides **1**(R^2=H), obtained only in the trans configuration,[12] reacted with amidine **a** or guanidine **b** by a selective nucleophilic attack on the ester group and afforded the intermediates **3** which evolved to **4**,[13] the only products observed are the 4-cyano-5-hydroxyimidazoles **4** and the aldehydes R^1CHO.

- On the other hand, when $R^2 \neq H$, the nitrile and the ester group of the tetrasubstituted epoxides **2**(R^1=R^2=CH_3 or Ph)[12] reacted both with the amidine **a** or the guanidine **b**, leading to a mixture of 4-hydroxy-5-cyanoimidazole **4** and 4-amino-5-carbethoxyimidazole **5**, we also observed the formation of ketone R^1R^2CO.[14]



Scheme

These experimental observations intimate that, depending on the steric hindrance of the epoxide, the amidine **a** or the guanidine **b** reacts either on the nitrile or on the ester group to give an intermediate such as **3**. Indeed we isolate **3**(R^1=$pClC_6H_4$, R^3=R^4=Ph) from the reaction of the epoxide **1**(R^1=$pClC_6H_4$, R^2=H) with the amidine **a**.[15] As expected, reflux of **3**(R^1=$pClC_6H_4$,R^3=R^4=Ph) in toluene leads to the imidazole **4a** and the aldehyde R^1CHO. Moreover partial thermolysis of the isolated intermediate **3**(R^1=$pClC_6H_4$,R^3=R^4=Ph) in ethanol

gave the epoxide **1**(R^1=pClC_6H_4, R^2=H) and the amidine **a**, beside the imidazole **4a**, showing the reversibility of the first step.

The course of the reaction of **1** with amidine **a** was different when NEt_3 was added in the reaction medium. In this case, the imidazoline **6a** which could be isolated,[16] was dehydrated in acidic medium to the imidazole **7a**.[17] The mechanism of this reaction is not yet established, we tentatively propose that the catalytic effect of NEt_3 can be accounted for by its reversible attack on the ester group allowing the ring opening of the epoxide to give the imidazoline **7a**.

In summary, we have shown that nucleophiles such as amidines or guanidines reacted chemoselectively with one functional group (cyano or ester) of the α-cyano epoxides **1** or **2**. The reaction opened a new route to substituted imidazoles : the 4-amino-5-carbethoxy or 4-hydroxy-5-cyano imidazoles or 4-carbethoxy-5-aryl-imidazoles. The observed chemoselectivity arises from the steric hindrance of the epoxides and from the presence or not of NEt_3 in the reaction medium.

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13. Preparation of **4** : A solution of epoxide **1**(R^1=pClC_6H_4, R^2=H)[12] (5mmol) and amidine **a** or guanidine **b** (5mmol) in toluene (50ml) was refluxed for 12h. The solvent was removed and the imidazole **4** precipitated by addition of petroleum ether, filtered and recrystallized in ethanol. R^1CHO was characterized by ^1H NMR. For example **4b:** mp.146°C. ^1H NMR ($CDCl_3$/TMS, 80MHz) : δ=7.32(m,10H) ppm. ^{13}C NMR ($CDCl_3$/TMS, 75MHz), δ=77, 115, 121, 122, 123, 126, 128, 129, 131, 134, 154, 168ppm. IR(Nujol) : ν=3200, 2200 cm^{-1}. HRMS calc. for $C_{16}H_{12}N_4O$ 276.297 found 276.301. Anal. calc. for $C_{16}H_{12}N_4O$ C 69.60 ; H 4.34 ; N 20.40 ; found C 69.68 ; H 4.23 ; N 20.27.
14. Preparation of **5** : A solution of epoxide **2**(R^1=R^2=CH_3 or Ph)[12] (5mmol) and amidine **a** or guanidine **b** (5mmol) in toluene (50ml) was refluxed for 96h. The solvent was removed and the imidazole **5** was precipitated by addition of ether, filtered and recrystallized in ethanol. Then the ether was evaporated and the imidazole **4** was precipitated by addition of petroleum ether. R^1R^2CO was characterized by ^1H NMR and by chromatography. For example **5a** : mp.182°C. ^1H NMR ($CDCl_3$/TMS, 80MHz) : δ=1.00(t,3H), 4.06(q, 2H), 7.25(m,10H)ppm. IR(Nujol) : ν=3500-3150, 1675 cm^{-1}. ^{13}C NMR ($CDCl_3$/TMS, 75MHz), δ=14, 59, 105, 128,128.5, 128.6, 128.7, 129, 129.2, 129.5, 138, 148, 155, 161ppm. HRMS calc. for $C_{18}H_{17}N_3O_2$ 307.132 found 307.132. Anal. calc. for $C_{18}H_{17}N_3O_2$ C 70.33 ; H 5.60 ; N 13.65 found C 70.43 ; H 5.81 ; N 13.50.
15. Formation of **3** : A solution of epoxide **1**(R^1=pClC_6H_4, R^2=H) (5mmol) and amidine **a** (5mmol) in toluene (50ml) was refluxed for 4h. The solvent was removed and the epoxide **3** was precipitated by addition of ether, filtered and recrystallized in ethanol. **3** (R^1=pClC_6H_4, R^3=R^4=Ph) : 55% yield. mp. 134°C. ^1H NMR ($CDCl_3$+CF_3CO_2H/TMS, 80 MHz) : δ=4.55(s, 1H), 7.47(m, 14H)ppm. IR(Nujol) : ν=3300, 2240, 1650 cm^{-1}.
16. Preparation of **6** : To a solution of epoxide **1**(R^1=pClC_6H_4 R^2=H) (5mmol) and amidine **a** (5mmol) in toluene (50ml) was added NEt_3 (15mmol) and the mixture was refluxed for 96h. The solvent was removed and the imidazoline **6** obtained as an oil. 90% yield. For example **6a**(R^1=pClC_6H_4) : ^1H NMR ($CDCl_3$+CF_3CO_2H/TMS, 80MHz) : δ=1.27(t, 3H), 4.27(q,2H), 5.45(s,1H), 7.32(m,14H)ppm. IR(Nujol) : ν=3200,1720 cm^{-1}
17. Preparation of **7** : The imidazoline **6** (5mmol) and acetic acid(2ml) in toluene(30 ml) was thermolyzed for 48h. The reaction mixture was diluted with Et_2O and washed with H_2O until pH 7. The extracts were dried and evaporated, the imidazole **7** was precipitated by addition of ether and recrystallized in ethanol. For example **7a**(R^1=pClC_6H_4) : 50% yield. mp. 172°C. ^1HNMR ($CDCl_3$/TMS, 80MHz) : δ=1.25(t, 3H), 4.32(q,2H), 7.22(m,14H) ppm. ^{13}C NMR ($CDCl_3$/TMS, 75MHz), δ=14, 60, 127,128, 128.1, 128.2,128.9, 129.2, 129.4, 129.5,130.4, 132, 132.2, 134, 136, 139, 148, 163ppm. IR (Nujol) : ν=1700 cm^{-1}. HMRS calc. for $C_{17}H_{21}N_3O$ 402.1135 found 402.114. Anal calc. for $C_{17}H_{21}N_3O$ C 71.54 ; H 4.75 ; N 6.95 ; Cl 8.80 found C 71.53 ; H 4.63 ; N 6.93 ; Cl 8.68.

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