A NOVEL SYNTHETIC ROUTE TO OXAZOLES: ONE POT SYNTHESIS OF 2-ARYLTHIO-5-ALKOXYOXAZOLES

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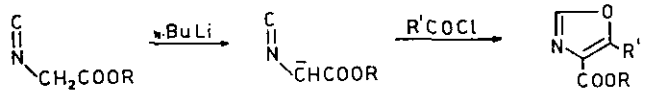
Abstract- Reaction between alkyl isocyanoacetates and arylsulfenyl chlorides afforded isothiocarbamoyl chlorides Ia-f which on treatment with triethylamine gave 2-arylthio-5-alkoxyoxazoles IIa-f in almost quantitative yields.

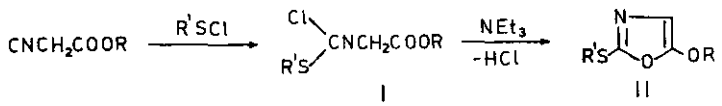
As is well known, alkyl isocyanoacetates have been largely employed in the synthesis of oxazole derivatives: treatment of alkyl isocyanoacetates with BuLi or *t*-BuOK gives the corresponding anions which react with acyl chlorides to give alkyl 5-substituted oxazole-4-carboxylates[1].



Although 5-alkoxyoxazoles and 2-alkyl- and arylthiooxazoles are two well known classes of compounds[2], no oxazole derivatives having both substituents were previously reported.

This paper deals with a novel synthetic method which allowed us to obtain 2-arylthio-5-alkoxyoxazoles, starting from alkyl isocyanoacetates, with the greatest ease. The synthesis was accomplished following the synthetic route described in Scheme 1.

Scheme 1

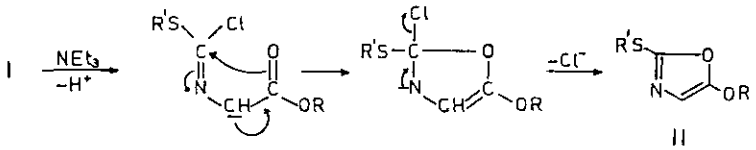


I II

a	R = Me	R' = 4-chloro-2-nitrophenyl		d	R = Et	R' = 4-chlorophenyl
b	R = Et	R' = 4-chloro-2-nitrophenyl		e	R = Et	R' = 4-methylphenyl
c	R = Et	R' = 2-nitrophenyl		f	R = Et	R' = phenyl

The first step consisted of the addition of arylsulfenyl chlorides to the carbenoid carbon of alkyl isocyanoacetates: this reaction occurred very easily to give N-alkoxycarbonyl-S-arylisothiocarbamoyl chlorides Ia-f in quantitative yields. The second step consisted of the cyclization of Ia-f with NEt_3: this reaction also occurred very easily and oxazoles IIa-f were obtained in almost quantitative yields. It must be noted that isolation of isothiocarbamoyl chlorides I is unnecessary: the cyclization with NEt_3 can be performed on the crude reaction mixture with equally good results. Compounds Ia-c were isolated and characterized: these products are rather stable and can be stored for long periods without decomposition.
In addition to the practical potentiality in the present synthesis, which readily provides 2-arylthio-5-alkoxyoxazoles in almost quantitative yields by an experimentally simple "one pot" procedure, this method has some interesting mechanistic features. A possible reaction pathway for the cyclization of isothiocarbamoyl chlorides I is reported in Scheme 2.

Scheme 2



The structure of compounds IIa-f was assigned on the basis of their ^{1}H-nmr and mass spectra. In the ^{1}H-nmr spectra of IIa-f a singlet signal at δ 6.10 - 6.38 was detected, due to the H-4 of the oxazole ring. In the mass spectra of IIa-f, besides the molecular ions, the fragment ion $[CH{=}C{-}OR]^+$ m/z 56 (R = Me) or m/z 70 (R = Et) was detected and this agrees with the formation of the oxazole ring. Furthermore the fragment ions $[4\text{-}ClC_6H_4SCO]^+$ m/z 171, $[4\text{-}MeC_6H_4SCO]^+$ m/z 151 and $[PhSCO]^+$ m/z 137 were detected in the mass spectra of IId, IIe and IIf, respectively.

EXPERIMENTAL

Melting points were obtained in open capillary tubes and are uncorrected. The ^{1}H-nmr spectra were recorded with a Perkin-Elmer R32 instrument for $CDCl_3$ solutions, chemical shifts are reported in ppm (δ) from TMS. The mass spectra were recorded with a Hewlett Packard 5790A GC MS instrument at 70 eV.
All of the compounds gave correct microanalyses.

2-Arylthio-5-alkoxyoxazoles (IIa-f)

General procedure- The calculated amount of the appropriate sulfenyl chloride in CH_2Cl_2 was slowly dropped into a solution of alkyl isocyanoacetate in CH_2Cl_2, maintaining the temperature at -50 °C. The resulting mixture was allowed to react at room temperature for 1 h[3], then cooled at -20 °C and treated with the calculated amount of NEt_3. The resulting mixture was allowed to react at room temperature for 1 h and then evaporated to dryness. The residue was stirred with Et_2O and then filtered. Evaporation of the filtrate left IIa-f in almost quantitative yields. IIa: mp 90-91 °C from MeOH; ^{1}H-nmr: 6.38(s,1H,H-4), 3.97(s,3H,CH_3); ms: $[M]^+$ m/z 286, $[R']^+$ m/z 156, $[M-R']^+$ m/z 130, $[N-CH=C-OMe]^+$ m/z 70, $[CH=C-OMe]^+$ m/z 56. IIb: mp 63-64 °C from MeOH; ^{1}H-nmr: 6.37(s,1H,H-4), 4.32-4.08(q,2H,CH_2), 1.50-1.34 (t,3H,CH_3); ms: $[M]^+$ m/z 300, $[R'S]^+$ m/z 188, $[R']^+$ m/z 156, $[M-R']^+$ m/z 144, $[CH=C-OEt]^+$ m/z 70. IIc: mp 66-67 °C from MeOH; ^{1}H-nmr: 6.36(s,1H,H-4), 4.34-4.08 (q,2H,CH_2), 1.52-1.36(t,3H,CH_3); ms: $[M]^+$ m/z 266, $[R'S]^+$ m/z 154, $[R']^+$ m/z 122, $[CH=C-OEt]^+$ m/z 70. IId: bp 140 °C/0.05 mm Hg; ^{1}H-nmr: 6.17(s,1H,H-4), 4.19-3.96 (q,2H,CH_2), 1.44-1.28(t,3H,CH_3); ms: $[M]^+$ m/z 255, $[R'SCO]^+$ m/z 171, $[R'S]^+$ m/z 143, $[R']^+$ m/z 111, $[CH=C-OEt]^+$ m/z 70. IIe: bp 124 °C/0.05 mm Hg; ^{1}H-nmr: 6.10(s,1H, H-4), 4.14-3.90(q,2H,CH_2), 2.28(s,3H,CH_3 toluene), 1.40-1.24(t,3H,CH_3); ms: $[M]^+$ m/z 235, $[R'SCO]^+$ m/z 151, $[R'S]^+$ m/z 123, $[R']^+$ m/z 91, $[CH=C-OEt]^+$ m/z 70. IIf: bp 122 °C/0.05 mm Hg; ^{1}H-nmr: 6.14(s,1H,H-4), 4.12-3.88(q,2H,CH_2), 1.37-1.21(t,3H, CH_3); ms: $[M]^+$ m/z 221, $[R'SCO]^+$ m/z 137, $[R'S]^+$ m/z 109, $[R']^+$ m/z 77, $[CH=C-OEt]^+$ m/z 70.

REFERENCES AND NOTES

* Author to whom correspondence should be addressed.

1. *See for example:* U.Schöllkopf and R.Schröder, *Angew.Chem.*, 1971, 83, 358; D. Hoppe, *Angew.Chem.Int.Ed.*, 1974, 13, 789; U.Schöllkopf, *ibid.*, 1977, 16, 339; S.Maeda, M.Suzuki, T.Iwasaki, K.Matsumoto, and Y.Iwasawa, *Chem.Pharm.Bull.*, 1984, 32(7), 2536.

2. I.J.Turchi, *Ind.Eng.Chem.Prod.Res.Dev.*, 1981, 20, 32; A.R.Katritzky and C.W. Rees,"Comprehensive Heterocyclic Chemistry", Vol.6, Part 4B, K.T.Potts, ed., Pergamon Press Ltd., Inc., Oxford, 1984, pp. 216-217.

3. Evaporation of this solution left isothiocarbamoyl chlorides Ia-f. Ia: mp 56-57 °C from petroleum ether (bp 40-70 °C); ^{1}H-nmr: 4.32(s,2H,NCH_2), 3.72(s,3H,CH_3). Ib: mp 52-53 °C from petroleum ether (bp 40-70 °C); ^{1}H-nmr: 4.28(s,2H,NCH_2). Ic: undistillable oil; ^{1}H-nmr: 4.26(s,2H,NCH_2).

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