A NEW TRANSFORMATION OF OXAZOLEACETATES INTO β-AMINOPYRROLES[1)]

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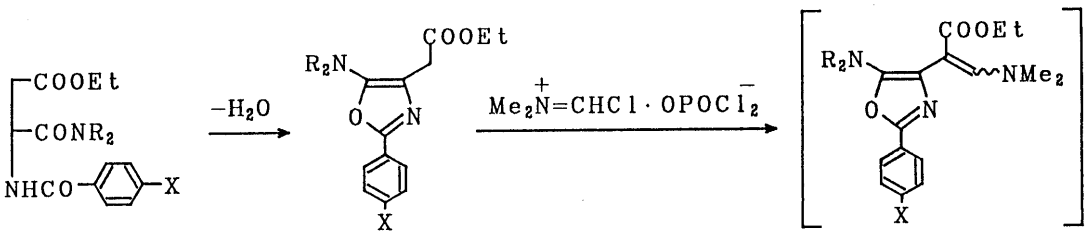
Ethyl 5-aryl-2-dialkylaminocarbonyl-4-dimethylamino-3-pyrrolecarboxylate (5) was expeditiously synthesized in good yields from aspartic acid diamide β-ester (1) using the Vilsmeier-Haack reagent *via* new oxazole-pyrrole ring transformation.

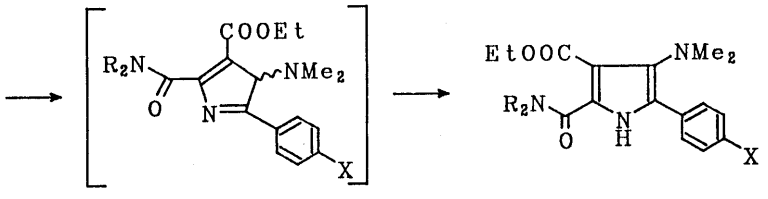
KEYWORDS oxazoleacetate; β-aminopyrrole; Vilsmeier-Haack reagent; ring transformation

Pyrroles are not only biologically useful compounds, they are also interesting from the viewpoint of organic reaction. The synthesis of pyrroles from other heterocyclic compounds have been devised; for example, isoxazole,[2)] isoxazoline,[3)] dihydrooxazine,[4)] pyridazine,[5)] aziridine,[6)] azirine,[7)] thiazine,[8)] dithiin,[9)] dihydropyridine,[10)] pyridinium salt,[11)] oxazepine,[12)] thiazole[13)] and oxazole[14)] have been transformed into pyrroles. Here we report a useful synthesis of β-aminopyrroles from aspartic acid diamide β-esters through a new ring transformation of oxazoleacetates.

In a previous paper,[15)] we reported the reactivity and usefulness of conjugated enamines [3-(aminomethylene)-3*H*-indoles] formed as an intermediate of the Vilsmeier-Haack reaction with indoles. In the course of our studies on the development of a new hypolipidemic agent,[16)] we synthesized ethyl 2-(4-chlorophenyl)-5-(1-pyrrolidinyl)-4-oxazoleacetate (**2a**) by the dehydrative cyclization of aspartic acid diamide β-ester (**1a**, NR_2=1-pyrrolidinyl, X=Cl) using polyphosphate ester (PPE). As an extension of these studies, we attempted to synthesize an enamine (**3a**) conjugated with an oxazole ring by a reaction of the Vilsmeier-Haack reagent with the active methylene group of **2a**.

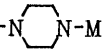


1a-c **2a-c** **3a-c**



4a-c **5a-c**

Table I. Synthesis of **5** from **1** [a)]

Compd.	$-NR_2$	X	Yield(%) [b)]	m.p.(°C)
5a		Cl	80	215–216
5b		Cl	82	198–199
5c		F	57	159–162
5d		Cl	95	232–233
5e	$-N(CH_2COOMe)_2$	H	78	102–103

a) All reactions were carried out at 60°C for 2 h using 3 molar eq. of $POCl_3$ in DMF.
b) Isolation yield.

This reaction was carried out in DMF at 0°C followed by stirring at 60°C for 2 h. However, the desired product **3a** was not isolated but ethyl 5-(4-chlorophenyl)-4-dimethylamino-2-(1-pyrrolidinyl)carbonyl-3-pyrrolecarboxylate (**5a**) was obtained in 71% yield. The structure of **5a** was determined by IR, ^{1}H-NMR, mass spectra and elemental analyses.[17)]

This unique pyrrole formation from the oxazole (**2a**) was not anticipated but it can be interpreted reasonably assuming the formation of contemplated conjugated enamine (**3a**) as follows. Under the reaction conditions which promote the formation of **3a**, it is transformed spontaneously into the pyrrole (**5a**) *via* 3*H*-pyrrole (**4a**) formed by a synchronous intramolecular attack of the enamine part in **3a** to the oxazole ring. From the viewpoint of enamine chemistry, such a reaction in which enamine directly attack a heterocycle is very interesting.

Since the Vilsmeier-Haack reagent is an excellent dehydrating agent, direct one-pot synthesis of **5a** from **1a** was readily designed. The dehydrative cyclization of **1a** to **2a** was accomplished at first using a reagent prepared with 1.2 molar equivalents of $POCl_3$ in DMF at 0°C. This afforded **2a** in 68% yield. A similar reaction of **1a** with 3 equimolar equivalents of $POCl_3$ in DMF at 60°C for 2 h resulted in the formation of **5a** in 80% yield as intended. This sequential formation of **2a** and **5a** from **1a** was clearly monitored by TLC analysis though neither **3a** nor **4a** was detected.

Furthermore, some aspartic acid diamide β-esters (**1b-e**) were similarly treated with excess Vilsmeier-Haack reagent to obtain the corresponding β-aminopyrroles (**5b-e**) in good yields as listed in the Table I. The multifunctional β-aminopyrroles obtained are also of great interest in biological activities, and some analogs prepared by the same reaction exhibited high hypolipidemic activities. Further work in this area will be reported elswhere.

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17) Spectroscopic data for (**5a**): IR(Nujol) ν: 3220, 1710, 1615cm^{-1}; ^{1}H-NMR($CDCl_3$) δ: 1.33(3H, t, J=7.5 Hz), 1.7-2.1(4H, m), 2.60(6H, s), 3.2-3.7(4H, m), 4.28(2H, q, J=7.5 Hz), 7.18 and 7.60(2H each, $A'_2B'_2$, J=9 Hz); Mass m/z: 389(M^+). Anal. Calcd. for $C_{20}H_{24}ClN_3O_3$: C, 61.61; H, 6.20; Cl, 9.09; N, 10.78. Found: C, 61.63; H, 6.19; Cl, 8.94; N, 11.01. All other compounds described herein gave satisfactory spectroscopic data and elemental analyses consistent with the structures assigned.

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