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A NOVEL PYRROLE SYNTHESIS VIA REACTION OF KETONES WITH N-AMINOIMIDES

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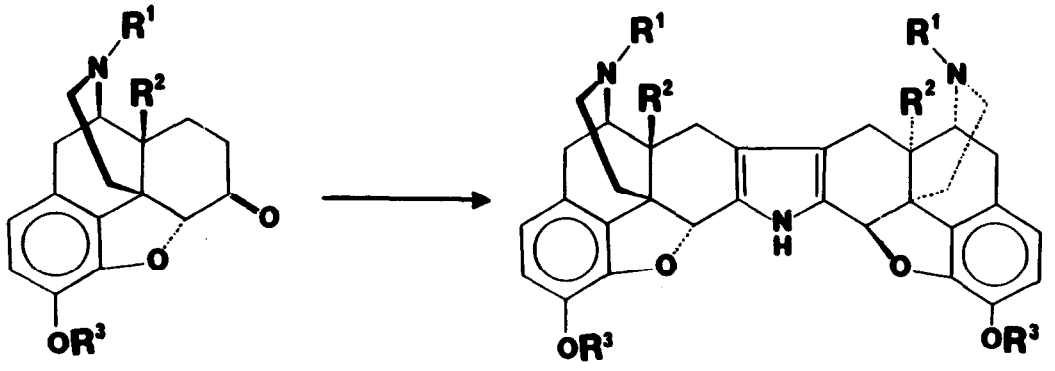
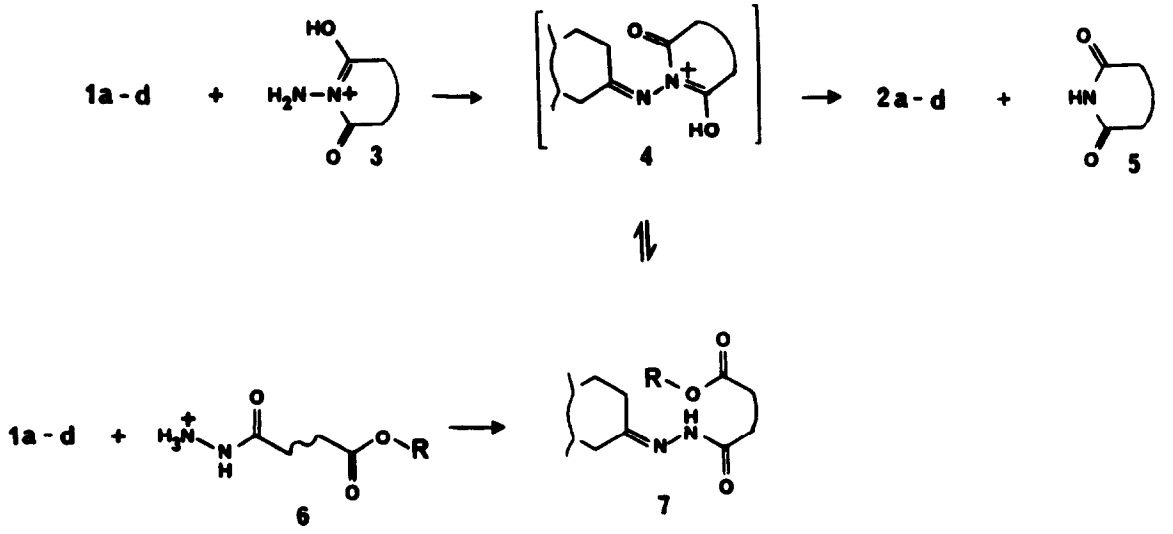
Summary: A new, mild synthesis of pyrroles using N-aminoimides and a ketone is described. The reaction has been utilized in the synthesis of dimeric morphinans containing a connecting pyrrole ring. The reaction appears to proceed through a diacylhydrazone intermediate, and it is suggested that the driving force behind the reaction is the facility with which a protonated imide moiety operates as a leaving group.

In the course of studies[3,4] on dimeric ligands with opioid antagonist activity, we sought a synthetic route to opiates that are connected by a rigid pyrrole ring 2. Symmetrically substituted pyrroles usually are prepared through variations of the Piloty synthesis using the respective azine as an intermediate.[5-7] However, the strong conditions of this reaction have excluded this as a method for a number of sensitive biologically active substances. Here we present a novel method for the synthesis of pyrroles under relatively mild conditions.



	R¹	R²	R³
a	$CH_2C_3H_5$	OH	H
b	CH_3	OH	H
c	CH_3	H	CH_3
d	CH_3	H	H

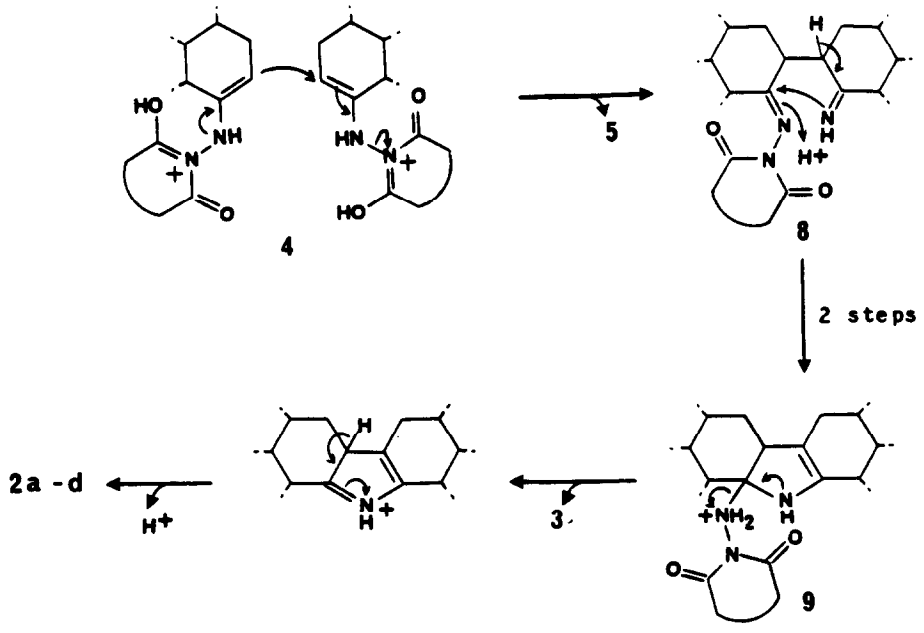
Our target compounds 2a-d were obtained from their respective morphinone hydrochlorides 1a-d and a N-aminoimide hydrochloride 3. The aminoimides react readily with the ketones 1 to form pyrroles 2a-d and imide 5, presumably via a diacylhydrazone intermediate 4 (Scheme 1). N-Aminosuccinimide or other N-aminoimides 3 can be used in this synthesis. Identification of the diacylhydrazone 4 intermediate derived from reaction of 1a was accomplished using N-aminophthalimide hydrochloride since it was capable of being isolated due to its precipitation from the reaction medium.[8]



Scheme 1.

In a typical procedure, a solution of naltrexone hydrochloride 1a (377 mg, 1 mmol) and N-aminosuccinimide hydrochloride 3[9] (150 mg, 1 mmol) in dimethylformamide (3 ml) was stirred for 0.5 h at 90°C. Aqueous 10% $NaHCO_3$ (50 ml) was added to the cooled solution and the precipitated crude product 2 was collected by filtration and purified on a silica gel column [EtOAc/NH_4OH/MeOH, 50:1:(0-5)]. After converting 2a to the hydrochloride salt, it was purified by gel filtration on Sephadex LH-20 in methanol: yield for 2a 60%; 2b 60%; 2c 48%; 2d 52%).[10] Other N-aminoimides, such as aminomaleimide hydrochloride or aminoglutarimide hydrochloride, have been found to be as effective as N-aminosuccinimide.

The reaction also can be conducted in methanol, ethanol, or other polar solvents. When methanol or other alcohols were employed, it was found that the monoacylhydrazone ester 7 was formed in equilibrium with diacylhydrazone 4. Indeed, we were able to synthesize 2a in comparable yield by conducting the reaction with succinylhydrazine ethyl ester hydrochloride 6 (R=C_2H_5) rather than aminosuccinimide. In this regard, we suggest that monoacylhydrazone 7 is formed and this then cyclizes to the diacylhydrazone 4, which is converted to the pyrrole 2. The fact that we were unable to effect the synthesis using monoacetylhydrazide strongly implicates the intermediacy of the diacylhydrazone intermediate 4. The mechanism for the



Scheme 2.

formation of the pyrrole 2 apparently does not involve an azine intermediate because subjecting naltrexone azine to conditions identical to those that effect conversion to 2 using our procedure does not result in any transformation.

If intermediate 4 is indeed required, then one reasonable pathway leading to 2a-d is outlined in Scheme 2. Since the N-aminoimide salt 3 appears to be protonated on the oxygen rather than its amino group,[11] this may explain why it is able to function as a leaving group in the hydrazone intermediate 4. Thus, the quaternary imide nitrogen would promote the departure of the imide moiety. Accordingly, we envisage the driving force for the dimerization to be the facile departure of the protonated imide leading to 8, which would then undergo cyclization to 9. Subsequently, the protonated diacylhydrazone moiety is envisaged to undergo elimination with the ultimate formation of the pyrrole ring.

To our knowledge, this is the first example in which a protonated imido moiety has been employed as a leaving group.

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10. The compounds have been characterized by correct elemental analysis, FAB MS, ^{1}H-NMR (all compounds have diagnostic shift of H-C_5: 2a - 5.49; 2b - 5.45; 2c - 5.55; 2d - 5.50 ppm in DMSO-d_6), ^{13}C-NMR (all 2 compounds have diagnostic shifts of C_6 and C_7: 2a - 121.37, 113.89; 2b - 121.43, 113.73; 2c - 115.25, 115.19; 2d - 118.92, 117.51 ppm in DMSO-D_6). The structure of compound 2a also has been proved by x-ray analysis (Z. Lipkowska, E.C. Etter, A.W. Lipkowski, P.S. Portoghese, "Abstract of Communications," ACA Annual Meeting, June, 1986, Hamilton, Canada).
11. Evidence for the unsymmetrical nature of 3 was obtained from the NMR spectrum of N-aminomaleimide hydrochloride, which exhibited nonequivalent vinyl proton resonances in DMSO, δ 6.41 (d, J=7Hz) and 7.61 (d, J=7Hz).

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