KNORR PYRROLE SYNTHESIS

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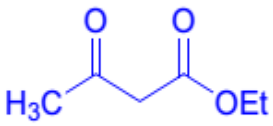
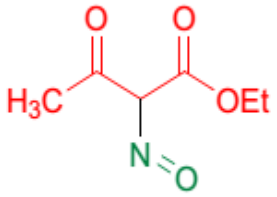
Knorr (1886):

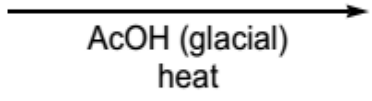


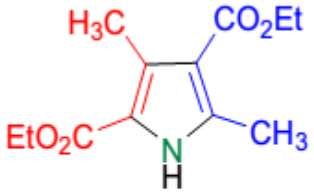
ethyl acetoacetate

+



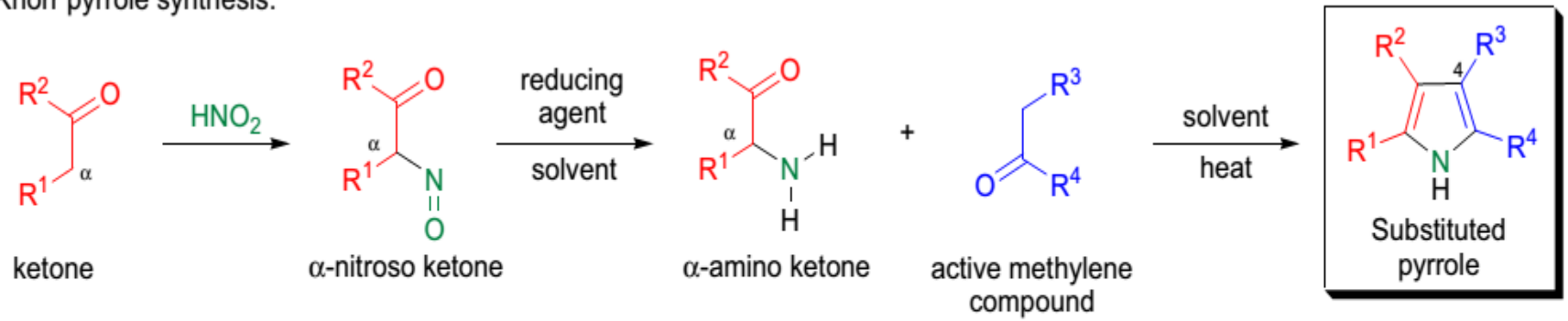
α-nitroso ethyl acetoacetate





3,5-dimethyl-1*H*-pyrrole-2,4-dicarboxylic acid diethyl ester

Knorr pyrrole synthesis:



ketone | α-nitroso ketone | α-amino ketone | active methylene compound | Substituted pyrrole

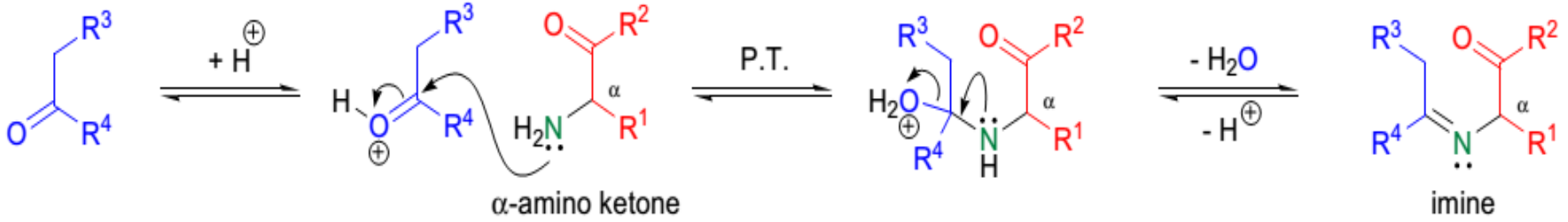
R^1 = H, aryl, CO_2R; R^2 = alkyl, aryl; R^3 = electron-withdrawing group (EWG) = COR, CO_2R, CN, SO_2R; R^4 = H, alkyl, aryl, CO_2R;
reducing agent: Zn/AcOH, $Na_2S_2O_4$, Pd(C)/H_2; solvent: AcOH, H_2O

The general features of these reactions are:

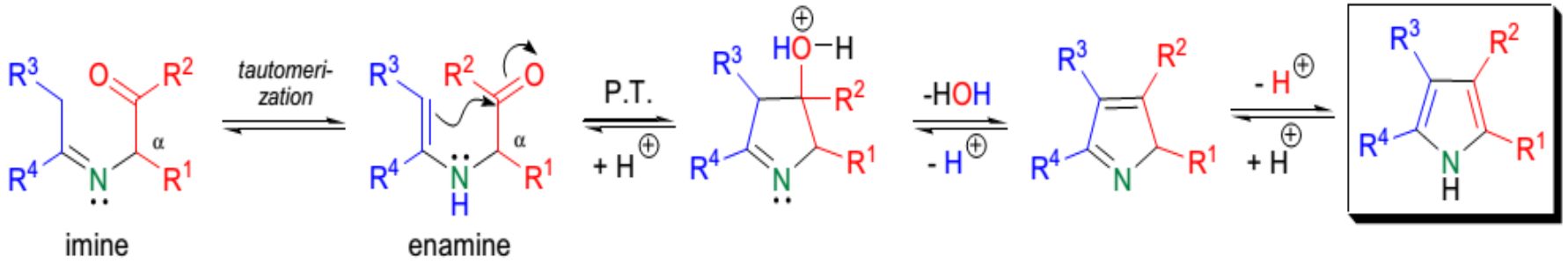
1) The reaction can be conducted under both acidic and basic conditions;
2) α-amino ketones are often quite labile and tend to undergo self-condensation (to form the corresponding pyrazines), so it is common to prepare them by first nitrosating the ketone and then reducing the resulting α-nitroso ketone in situ;
3) the reduction of the α-nitroso ketone (or α-oximino ketone in its tautomerized form) is conducted using zinc powder in acetic acid, aqueous solution of sodium dithionate (Na2S2O4), or catalytic hydrogenation under which conditions ketones and esters are not reduced;
4) the hydrochloride salts of α-amino ketones are stable, and they can be used directly and the HCl can be neutralized in situ;
5) carbonyl-protected (e.g., acetal) derivatives of α-amino ketones are often utilized to avoid selfcondensation;
6) alternatively the required α-amino ketones can be prepared by the Neber rearrangement of Oacylated ketoximes;
7) N-substituted pyrroles are formed when a secondary amino ketone is used;
8) the active methylene component is usually a 1,3-diketone, β-ketoester or a β-cyanoester;
9) if the active methylene compound is not reactive enough, the formation of the pyrrole will be slow and the self-condensation of the α-amino ketone becomes predominant;
10) when non-symmetrical ketones are used, there is a modest regioselectivity favoring the regioisomer in which the bulkier group is part of the acyl substituent at C4.

Mechanism: [18-20]

Condensation of the amino ketone and ketone to give an imine:

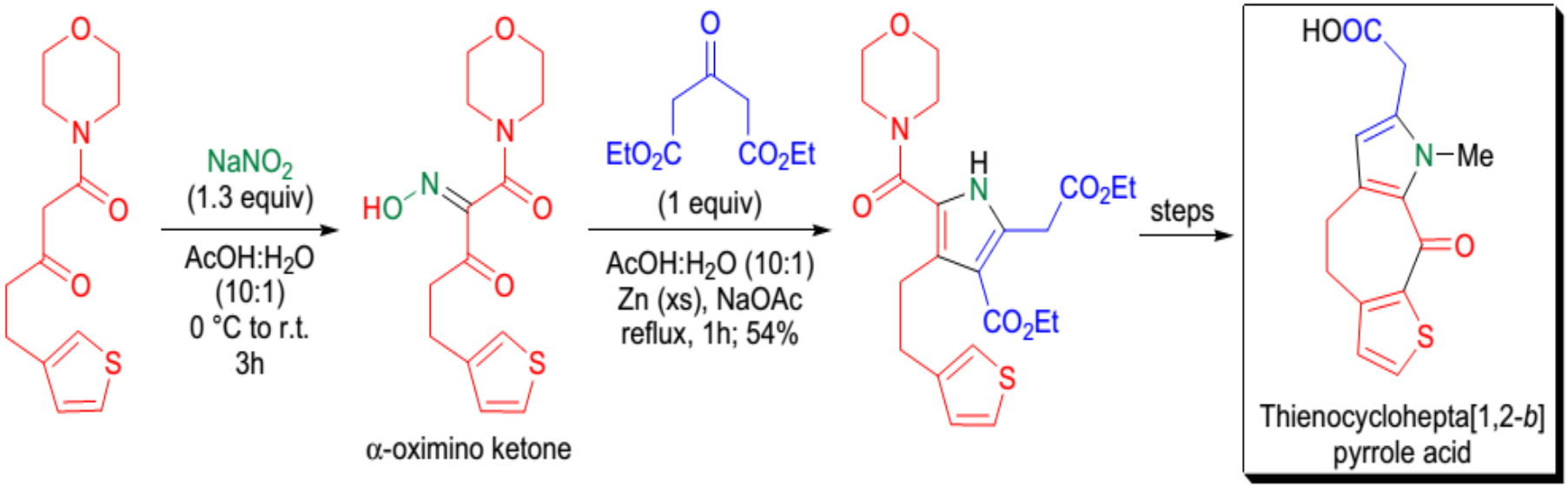


Tautomerization of the imine to the enamine and cyclization:

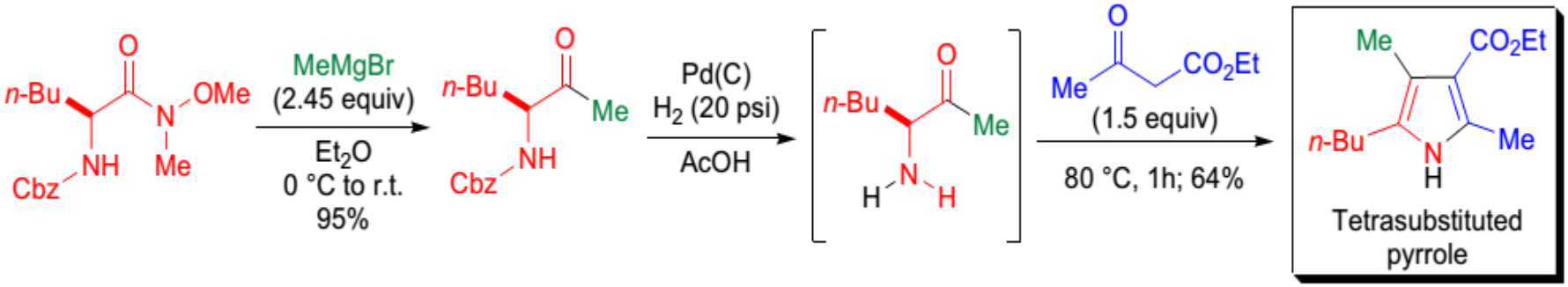


Synthetic Applications:

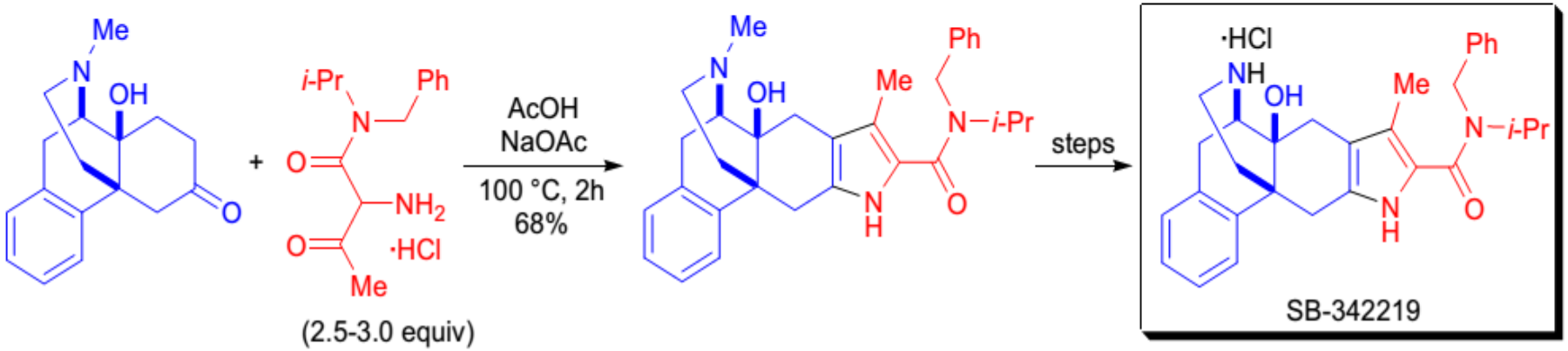
A new anti-inflammatory/analgesic agent, 4,5,8,9-tetrahydro-8-methyl-9-oxothieno[3',3':5,6]cyclohepta[1,2-*b*]-pyrrole-7-acetic acid, was synthesized by H.E. Rosenberg and R.W. Ward et al. using the *Knorr pyrrole synthesis* for the construction of the highly substituted pyrrole ring.[21] The starting β-ketoamide was first nitrosated under standard conditions in acetic acid/water to afford the corresponding α-oximino ketone. This was followed by the addition of diethyl acetone-1,3-dicarboxylate, zinc powder, and sodium acetate, and the resulting mixture was heated at reflux. The cyclization to obtain the desired tricyclic ketone was achieved under Vilsmeier-Haack conditions using $POCl_3$.



- A useful modification of the Knorr pyrrole synthesis was developed in the laboratory of J.M. Hamby for the construction of tetrasubstituted pyrroles. The necessary α-amino ketones were prepared from N-methoxy-Nmethylamides of amino acids (Weinreb amides).13 These Weinreb amides were prepared by the mixed anhydride method and treated with excess methylmagnesium bromide in ether to afford the corresponding Cbz-protected α-amino ketones in excellent yield. The Cbz group is removed by catalytic hydrogenation in the presence of the active methylene compound (e.g., acetoacetic ester), the catalyst is then filtered and the resulting solution is heated to reflux to bring about the condensation.



The large-scale synthesis of a potent δ-opioid antagonist, SB-342219, was accomplished by the research team of J.S. Carey.[22] The route developed by medicinal chemists could not be fully adapted for the large-scale preparation, since it required the addition of finely divided zinc powder in portions to a hot and flammable solvent containing a phenylhydrazone and a low concentration of the resulting α-amino ketone had to be maintained. Therefore, a procedure was sought that avoided the use of zinc metal altogether. The tricyclic ketone was mixed with an excess of the amino ketone hydrochloride in acetic acid and heated. Only one regioisomer of the pyrrole was formed in good yield, which was then converted to the final compound in a few steps.



The two-step one-pot total synthesis of Ro 22-1319, an antipsychotic agent featuring a rigid pyrrolo[2,3-*g*]isoquinoline skeleton, was accomplished by D.L. Coffen and co-workers.[23] The cyclic 1,3-diketone precursor was prepared from arecoline and dimethyl malonate, and in the same reaction vessel an amino ketone hydrochloride was added. The pH of the reaction mixture was adjusted to 4 in order to initiate the formation of the pyrrole.