Ready Decarboxylation of Imines of α-Keto Acids. Mechanism and Application to Thioamide Synthesis

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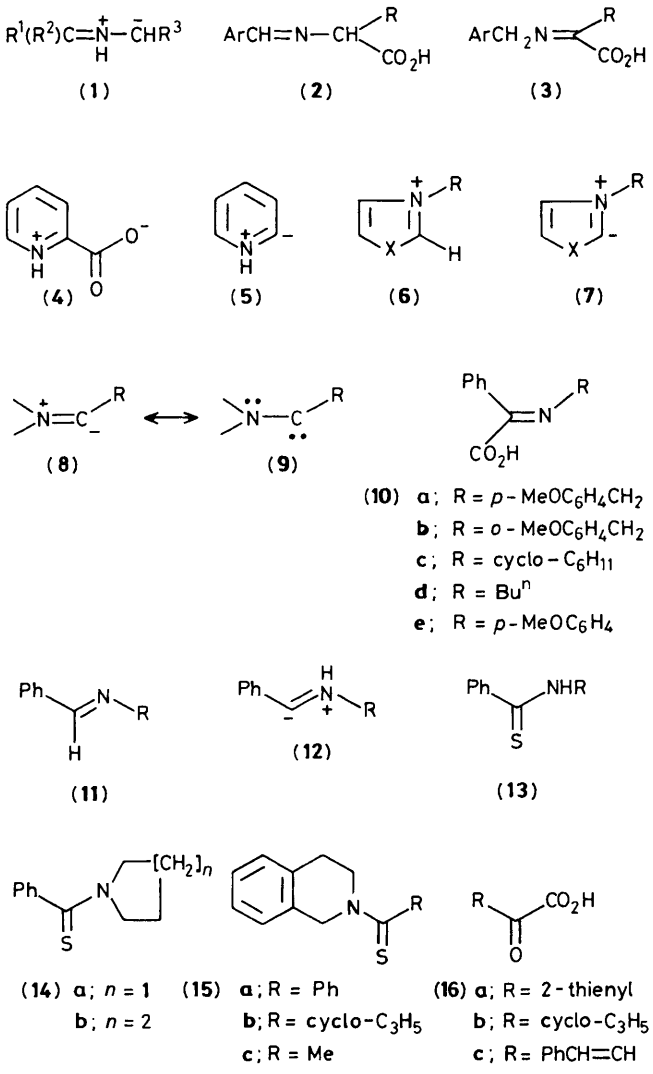
α-Keto acids are readily decarboxylated *via* imine formation with primary and/or secondary amines even when imine–enamine isomerisation can occur; the process is thought to involve an intermediate zwitterion which can be trapped by sulphur to give thioamides in excellent yield.

We have recently shown that decarboxylative transamination involving α-amino acids and carbonyl compounds proceeds *via* 1,3-dipolar species (**1**) and that these can be trapped by a wide range of dipolarophiles.[1,2] Species analogous to (**1**) may thus occur in decarboxylative transamination processes mediated by pyridoxal phosphate. The related biochemical transamination of α-amino acids by pyridoxal enzymes involves prototropy, rather than decarboxylation, of the initial imine, (**2**) → (**3**).[3] The isomeric imine (**3**) is an imine of an α-keto acid. Non-oxidative enzyme catalysed decarboxylation of α-keto acids to aldehydes involves adduct formation with thiamine pyrophosphate and it is generally considered that



this is essential because α-keto acids lack a suitable electron sink to stabilize negative charge development during decarboxylation.[4,5] However, it is well known that pyridine-2-carboxylic acid undergoes decarboxylation *via* the zwitterion (**4**) to give (**5**) which can be trapped by aldehydes and other electrophiles (Hammick reaction).[6] Furthermore, the ready deprotonation of azolium cations (**6**) at C(2)[5] to give (**7**) is the basis of the biochemistry of thiamine pyrophosphate[4] and important synthetic methodology for C–C bond formation.[7] Thus the moiety (**8**) possesses intrinsic stabilising features when part of an aromatic ring system in which R is a heteroatom or an sp^2 carbon centre. This enhanced stability is usually attributed to carbene resonance, (**8**) ⟷ (**9**), but it is unclear if the presence of the ring provides additional stability.

Acyclic examples of (**8**) might be generated by decarboxylation of imines of α-keto acids and this encouraged us to investigate a series of such imines in some of which 1,3-dipole formation might also occur. Three types of imine (**10a—e**) have been studied: those, (**10a,b**), in which imine isomerisation, followed by prototropy, might lead to 1,3-dipole formation,[8] imines (**10c,d**) of primary aliphatic amines, and the imine (**10e**) of a primary aryl amine. Decarboxylation of (**10a,c,d**) to (**11a,c,d**) occurred smoothly in boiling benzene† in <0.5 h whilst that of (**10e**) to (**11e**) took *ca.* 5 h. Formation of the corresponding 1,3-dipole (**1**, R^1 = H, R^2 = Ph, R^3 = *p*-$MeOC_6H_4$) in the case of (**10a**) was ruled out by negative trapping experiments with *N*-phenylmaleimide and the clean decarboxylation of (**10a**, CO_2D deuteriated) to (**11a**, CD=N) with no deuterium incorporation in the benzylic methylene group of (**11a**). Decarboxylation can be achieved at lower temperatures and without preformation of the imine. Thus, benzoylformic acid and benzylamine (CH_2Cl_2, 40 °C, 3 h) give a quantitative yield of (**11**, R = CH_2Ph). The mechanism is believed to be analogous to that of the Hammick reaction and to involve the zwitterion (**12**). Attempts to trap (**12a—e**) with aromatic aldehydes were unsuccessful.‡ However, reaction of (**10a—d**), or an equimolar mixture of amine and benzoylformic acid, with a 10 molar excess of sulphur in benzene (80 °C, 20 min) gave the corresponding thioamides (**13a—d**) in 70—80% yield, together with some imine (**11a—d**). Trapping of azolium ylides (**7**) with sulphur has been reported previously.[9]

Similar reactions can be carried out with secondary amines. Thus pyrrolidine, benzoylformic acid, and 10 mol equiv. of sulphur on heating in boiling benzene for 10 min gave a quantitative yield of (**14a**). Similarly, piperidine (benzene, 80 °C, 1 h) gives (**14b**) and tetrahydroisoquinoline (benzene, 80 °C, 15 min) gives (**15a**). The thienyl, cyclopropyl, and styryl α-keto acids (**16a—c**) react in an analogous way with primary and secondary amines; *e.g.* (**16b**), tetrahydroisoquinoline, and 10 mol equiv. of sulphur (benzene, 15 min) give a quantitative yield of (**15b**). In contrast pyruvic acid, primary amines, and sulphur give complex mixtures, but with tetrahydroisoquinoline the thioamide (**15c**) (75%) is obtained.

Thus it appears that α-keto acids can be readily decarboxylated *via* imine formation with primary and/or secondary amines even when isomerisation to the corresponding enamine can occur.

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† The reaction will work in toluene but benzene combines good solvent properties and low boiling point.

‡ Transimination and competitive proton transfer, (**12**) → (**11**), intervene.