Ready Decarboxylation of Imines of α-Keto Acids. Mechanism and Application to Thioamide Synthesis
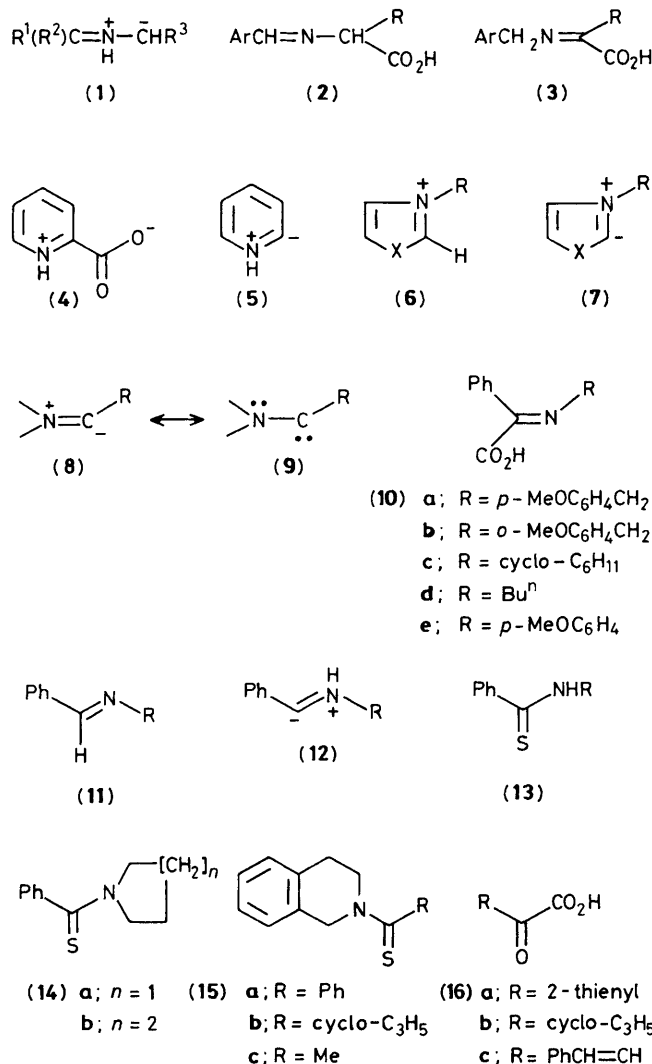
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α-Keto acids are readily decarboxylated *via* imine formation with primary and/or secondary amines even when imine–enamine isomerisation can occur; the process is thought to involve an intermediate zwitterion which can be trapped by sulphur to give 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

$R^1(R^2)C=\overset{+}{\underset{H}{N}}-\bar{C}HR^3$ (1)

$ArCH=N-CH\overset{R}{\underset{CO_2H}{\diagup}}$ (2)

$ArCH_2N=\overset{R}{\underset{CO_2H}{\diagdown}}$ (3)

(4) (5) (6) (7)

$>\overset{+}{N}=C\bar{-}R \longleftrightarrow >\overset{\cdot\cdot}{N}-\overset{\cdot\cdot}{C}\overset{\cdot\cdot}{-}R$

(8) (9)

$Ph\diagdown\overset{}{\diagup}=N-R$ with CO_2H (10)

(10) **a**; R = p-MeOC$_6$H$_4$CH$_2$
b; R = o-MeOC$_6$H$_4$CH$_2$
c; R = cyclo-C$_6$H$_{11}$
d; R = Bu^n
e; R = p-MeOC$_6$H$_4$

(11) (12) (13)

(14) **a**; $n = 1$ (15) **a**; R = Ph   (16) **a**; R = 2-thienyl
b; $n = 2$ **b**; R = cyclo-C$_3$H$_5$ **b**; R = cyclo-C$_3$H$_5$
   c; R = Me   **c**; R = PhCH=CH

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) $\longleftrightarrow$ (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$_6$H$_4$) in the case of (10a) was ruled out by negative trapping experiments with N-phenylmaleimide and the clean decarboxylation of (10a, CO$_2$D deuterated) 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$_2$Cl$_2$, 40 °C, 3 h) give a quantitative yield of (11, R = CH$_2$Ph). 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.

References

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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.