Formation of [2+2] Cycloadducts from Heterocyclic Formamidines and Phenyl Isocyanate

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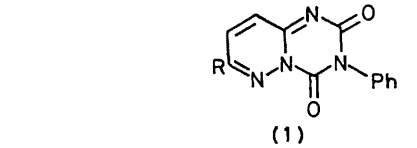
Summary Heterocyclic formamidines react with phenyl isocyanate at room temperature to give a [2 + 2] cycloadduct which decomposes at elevated temperatures in two different ways; phenyl isocyanate reacts with the heterocyclic isocyanate formed *in situ* to form a new cycloadduct, a fused 1,3,5-triazine-2,4-dione derivative.

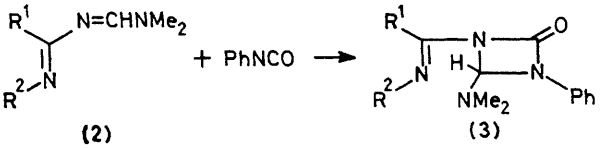
IN general, imines react with isocyanates *via* 1,4-dipolar intermediates to give 1,3-diazetidinones (1:1 adducts) or else react further with another molecule of the starting imine or isocyanate to give 1,3,5-triazines (1:2 or 2:1 adducts).[1] Exceptions have been recorded for some isocyanates or arylsulphonylimines[2] and aldazines,[3] and [2 + 2] cycloadditions, except with ketens, have been recorded in only a few cases.[4]

Trisubstituted formamidines give 1,3,5-triazines on reaction with aromatic isocyanates (1:2 adducts)[5] and methyl *N*-t-butylformimidate reacts similarly.[6] *NN*-Dimethyl-*N'*-(Δ^2-thiazolin-2-yl)formamidine gives a 1:2 adduct at 80 °C, whereas at room temperature a 1:1 cycloadduct is formed with phenyl isocyanate. In both cases 1,3,5-triazines are formed.[7]

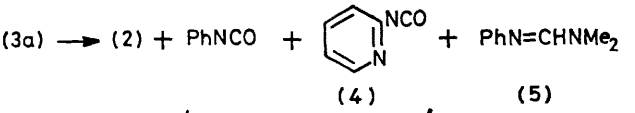
Recently, we reported the synthesis of pyridazino[2,3-*a*]-1,3,5-triazines (**1a**, **b**).[8] One method involved the reaction of *NN*-dimethyl-*N'*-(pyridazin-3-yl)formamidine, or its 6-chloro analogue, with phenyl isocyanate upon heating. We have now obtained evidence that this reaction, when conducted in methylene chloride at room temperature gives first a [2 + 2] cycloadduct (**3**) {*e.g.*[†] (**3a**) (91% yield), m.p. 190 °C, *m/e* 268(M^+); (**3b**) (86% yield), m.p. 96—98 °C; ^{1}H n.m.r. ($CDCl_3$) δ 7·80 (s, 5-H), 8·28 (s, C*H*NMe_2), 2·95 (s, Me_2), 6·70—7·35 (m, Ph), 8·70 (s, NH), 4·09 (q, CO_2CH_2Me), and 1·28 (t, CO_2CH_2*Me*), J_{Et} 6·5 Hz; *m/e* 329 (M^+); (**3c**) (88% yield) m.p. 134—135 °C (decomp.); ^{1}H n.m.r. ($CDCl_3$) δ 6·28 (s, 5-H), 8·25 (s, C*H*NMe_2), 2·95 (d, NMe_2), 2·25 (s, 4- and 6-Me), and 6·55—7·25 (m, Ph); *m/e* 297}. At elevated temperatures cycloreversion occurs in two different ways and subsequent [2 + 4] cycloaddition of the two isocyanate units formed gives (**6**) in 78% yield, m.p. 252—256 °C (decomp.) [lit.[9] 250—255 °C (decomp.)]; ^{1}H n.m.r. [$(CD_3)_2SO$] δ 7·88 (ddd, 5-H), 6·52 (ddd, 6-H), 7·40 (ddd, 7-H), 6·70 (ddd, 8-H), and 6·8—7·1 (m, Ph), $J_{5,6}$ 6·9, $J_{5,7}$ 1·6, $J_{5,8}$ 0·8, $J_{6,7}$ 6·6, $J_{6,8}$ 1·5, and $J_{7,8}$ 8·4 Hz; *m/e* 239(M^+).



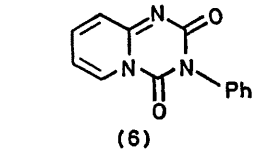
(1)
a; R=H
b; R=Cl



(2) (3)
a; R^1R^2=
b; R^1R^2= EtO_2C
c; R^1R^2=



(4) (5)



(6)

In this manner, the cycloadduct (**3**) gives, upon heating, a mixture of the original reactants and, in addition, the heterocyclic isocyanate and *NN*-dimethylaminomethyleneaniline (**5**). This decomposition could be monitored by an n.m.r. probe, *e.g.*, when using 2-(*NN*-dimethylaminomethyleneamino)-4,6-dimethylpyrimidine and phenyl isocyanate as starting material the presence of (**5**) could be

detected in the reaction mixture. Although heteroaryl isocyanates are known to be unstable and homodimerize into 1,3,5-triazines,[9] in the present case the heterocyclic isocyanate formed *in situ* reacted in a [2 + 4] cycloaddition with phenyl isocyanate to give the bicyclic adduct (**6**). The adduct (**3c**), however, when heated under reflux in diethyleneglycol dimethyl ether for 1 h, decomposed into 2-amino-4,6-dimethylpyrimidine.

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