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A SIMPLE PREPARATION OF 1,3,5-TRIAZINE DERIVATIVES FROM 4-PYRIDONES

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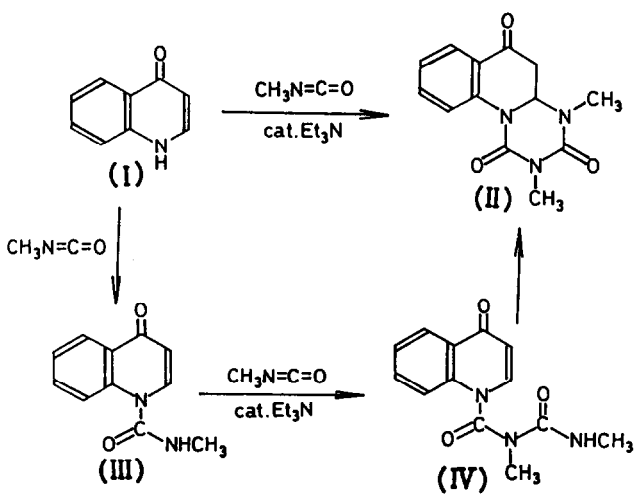
abstract: The reaction of 4-pyridone or 4-quinolone with methyl or benzyl isocyanate in the presence of triethylamine or 1,1,3,3-tetramethylguanidine base gave the corresponding 1,3,5-triazine derivative (e. g., II) in a good yield via stepwise additions.

In connection with our studies on reactivities of N-containing heteroaromatics,[1,2,3] we have found that 4-pyridone or 4-quinolone, as a heterocumulenophile, affords a 1,3,5-triazine derivative, whose ring system is of importance in physiologically active substances. We now wish to report a simple, easy route to 1,3,5-triazine derivatives from 4-pyridones via the combination of stepwise additions and an intramolecular Michael addition, as a new entry into 1,3,5-triazine derivatives.[4,5,6]



To a DMF (10 ml) solution of 4-quinolone (I) (1.00 g, 7 mmol) containing a few drops of triethylamine (TEA) was added methyl isocyanate (MeNCO) (0.97 g, 17 mmol) dropwise at room temperature under nitrogen atmosphere. The solution was stirred for 24 h under the above conditions and then poured into water (50 ml). Recrystallization of the precipitate (crude 1.58 g, 88% yield) from MeOH-$CHCl_3$ gave colorless needles, mp 185.5-186.0 ^{o}C, whose structure was confirmed as 1:2 cycloadduct (II) on the basis of analytical and spectral data.[7)]

In order to elucidate the reaction pathway to II, the reaction of I (1.00 g, 7 mmol) with excess MeNCO (5.5 g, 96 mmol) in the absence of TEA was examined with stirring for 24 h at r.t. under N_2. After evaporation of MeNCO, 1:1 adduct (III), mp 203-204 ^{o}C, was obtained in a 95% yield. As a next step, a few drops of TEA were added to a suspension of III (0.30 g, 1.5 mmol) in excess MeNCO. After stirring for 3 days at r.t. under N_2, III was converted to II even under such heterogeneous conditions in a 32% yield.

The results imply that the reaction proceeds via TEA-base catalyzed stepwise addition of MeNCO (1:1 adduct (III) to 1:2 acyclic adduct (IV)) and an intramolecular Michael addition to afford a triazine ring. In fact, the stepwise conversion of I to II via III and IV in a DMF solution was confirmed by analytical HPLC and preparative GPC experiments. The 1:2 acyclic adduct (IV) could be isolated and identified on the basis of ^{1}H and ^{13}C-NMR data.[8)]

Fig. 1 shows a composition-reaction time profile of the four corresponding compounds, I, II, III, and IV. Here, one example for the reaction of I (0.50 g), MeNCO (0.47 g), and TEA (35 mg) in DMF (7.5 ml) was illustrated. Toluene (ca. 1.5 ml) was added as an internal reference of HPLC analyses.

Similarly, 4-pyridone reacted with MeNCO under similar conditions to give the corresponding type-III and type-II (mp 167.0-167.5 ^{o}C)[9)] compounds in a 91% and 75% yield, respectively. In contrast to the 4-pyridone case, Kelyman reported that the reaction of certain substituted 2-pyridones with MeNCO under similar conditions gave the corresponding 1:1 adduct, that is, either N-methyl-2-oxo-1(2H)pyridinecarboxyamide or 2-pyridylcarbamate,

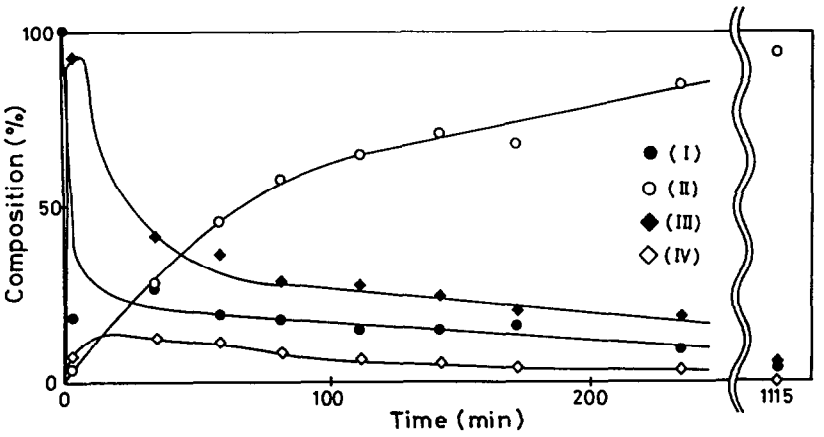


Fig. 1 A composition-reaction time profile for the reaction of 4-quinolone

depending on the position and the nature of substituents.[10] The reaction of 3-nitro-4-pyridone with MeNCO was examined under similar conditions to see if a substituent causes a change in the reaction product as above. However, no reaction occurred in this case even with prolonged stirring for 16 days.

The reactions of 4-quinolone with a variety of isocyanates were carried out under the same conditions as those with MeNCO. Benzyl isocyanate successfully gave the corresponding type-II compound, mp 146-147 ^{o}C,[11] in a 54% yield (stirring for 4 days). Isopropyl isocyanate failed to give not only type-II compound, but also type-III compound in the absence of TEA. Phenyl isocyanate trimerized to give a known cyclic adduct by itself with a TEA-base catalyst.

Finally, we found that the formation of II was subject to base catalysis. Analytical HPLC monitorings told us that boron trifluoride etherate, a Lewis acid, did not proceed the reaction to II, but an increase in the concentration of TEA base accelerated the conversion rates, especially from III to IV and II for the reaction of I with MeNCO. A stronger base such as 1,1,3,3-tetramethylguanidine gave much more acceleration of the overall reaction; stirring for 3 minutes yielded a 95% conversion for II.

Thus, the principal features of the present triazine ring formation reaction which we found were clarified. Further studies are in progress.

References and Notes

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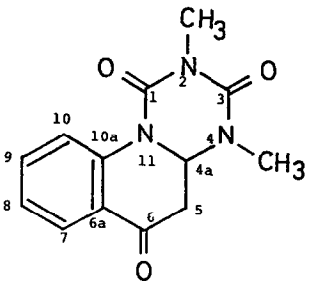
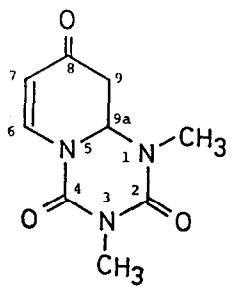
7) IR(nujol) 1710, 1670, 1600 cm^{-1}(C=O); H-NMR ($CDCl_3$) δ=8.08-7.30(4H, m, Ar), 5.17(1H, dd, J=13.0 and 2.1 Hz, C$\underline{H}$), 3.29(3H, s, C$\underline{H_3}$), 3.09 (3H, s, C$\underline{H_3}$), 2.93(1H, dd, $J_{5,5'}$=16.9, $J_{5,4a}$= 13.0 Hz, C$\underline{H}$H), 3.04(1H, dd, $J_{5,5'}$=16.9, $J_{5',4a}$ =2.1 Hz, CH$\underline{H}$); ^{13}C-NMR($CDCl_3$) δ=190.9(C-6), 150.5 and 150.3(C-1, C-3), 141.7(C-10a), 134.6 (C-9), 127.3, 126.5, and 126.4(C-7, C-8, C-10, C-6a), 68.8(C-4a), 43.3(C-5), 32.5 and 28.8 (two CH_3).



8) H-NMR($CDCl_3$) δ=8.43-7.33(4H, m, Ar), 8.41(1H, br. s, NH), 7.68(1H, d, J=8.1 Hz, N-CH=), 6.40 (1H, d, J=8.1 Hz, =CH-CO), 3.14(3H, s, $CONCH_3CO$), 2.98(3H, d, J=4.6 Hz, NH-C$\underline{H_3}$).



9) IR(nujol) 1720, 1660, 1620 cm^{-1}(C=O); UV_{max}(MeOH) 287.5 nm (ε 14000); MS(70 eV), m/e, 209(M^+); H-NMR($CDCl_3$) δ=8.13(1H, d, J=8.3 Hz, N-C$\underline{H}$=CHCO), 5.58(1H, dd, J=8.3 and 1 Hz, N-CH=C$\underline{H}$CO), 5.12 (1H, dd, J=12.9 and 4.9 Hz, C$\underline{H}$), 3.30(3H, s, C$\underline{H_3}$), 3.04(3H, s, C$\underline{H_3}$), 2.99(1H, ddd, $J_{9,9'}$=15.6, $J_{9,9a}$=4.9, $J_{9,7}$=1 Hz, C$\underline{H}$H), 2.76(1H, dd, $J_{9,9'}$=15.6, $J_{9',9a}$12.9 Hz, CH$\underline{H}$); ^{13}C-NMR($CDCl_3$) δ=189.9(C-8), 151.6 and 148.7(C-2, C-4), 141.1(C-6), 108.4(C-7), 66.6(C-9a), 41.6(C-9), 30.1 and 29.2(two CH_3). Anal., Found: C, 51.46; H, 5.18; N, 19.90%. Calcd for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09%.

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11) IR(nujol) 1710, 1670, 1600 cm^{-1}(C=O); MS(70 eV), m/e, 411(M^+).

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