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RING TRANSFORMATION REACTION OF 1,2,4,5-TETRAZINES TO 4-AMINOPYRAZOLES BY CYANOTRIMETHYLSILANE

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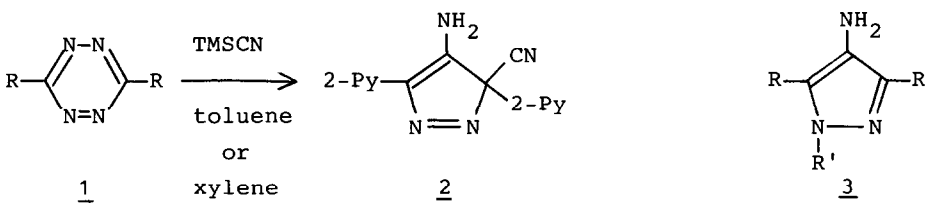
Abstract: 3,6-Disubstituted 1,2,4,5-tetrazines reacted with cyanotrimethylsilane in toluene or xylene to give 3,5-disubstituted 4-amino-3-cyano-3H-pyrazole, 4-amino-1-arylmethyl-1H-pyrazoles, or 4-amino-1H-pyrazole.

Cyanotrimethylsilane (TMSCN) was shown by Ojima et al.[1] to react with Schiff bases to give α-aminonitriles. The reaction was extended to α,β-unsaturated imines[2] for the preparation of β,γ-unsaturated α-amino acids.[3] However, it was necessary for C=N bonds of heteroaromatic compounds to be activated by N-acylation or N-oxidation prior to attack of TMSCN. Thus, many Reissert compounds[4] were prepared, and N-oxides of pyridines[5] and pyrimidines[6] underwent nucleophilic substitution similarly to the conversion of nitrones to α-iminonitriles.[7] Now we wish to report a novel ring transformation reaction of 1,2,4,5-tetrazines to 4-amino-3H or 1H-pyrazoles by TMSCN, which appears to occur by the initial addition of TMSCN to the C=N bond of tetrazines.

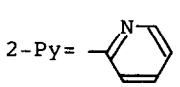
A mixture of 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine (1a) (1.0 mmol) and TMSCN (2.0 mmol) in toluene (15 ml) was refluxed for 7 h under nitrogen.

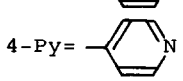
Scheme 1



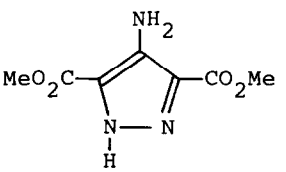
1 2 3

1	R
a	2-Py
b	4-Py
c	CO_2Me

2-Py= 

4-Py= 

(21%)



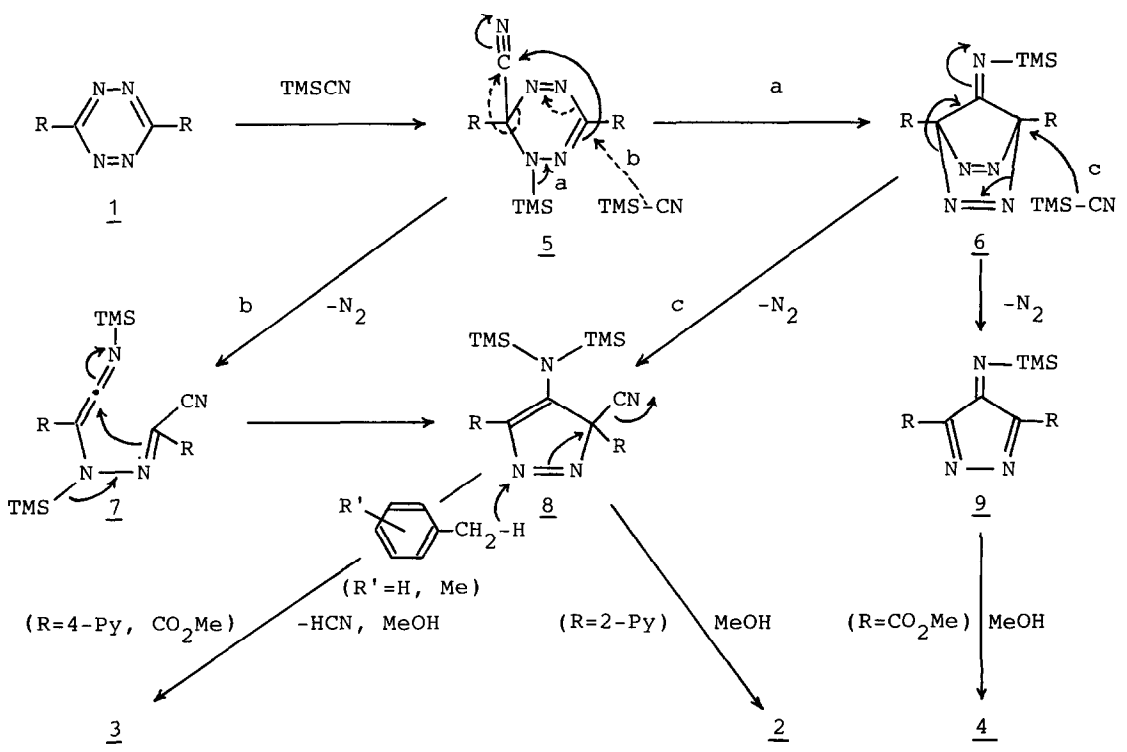
4

(21-35%)

3	R	R'	Yield (%)
a	4-Py	$C_6H_5CH_2$	44
b	4-Py	o-$MeC_6H_4CH_2$	55
c	4-Py	m-$MeC_6H_4CH_2$	44
d	4-Py	p-$MeC_6H_4CH_2$	52
e	CO_2Me	$C_6H_5CH_2$	4
f	CO_2Me	o-$MeC_6H_4CH_2$	5
g	CO_2Me	m-$MeC_6H_4CH_2$	14
h	CO_2Me	p-$MeC_6H_4CH_2$	17

After evaporation of the solvent, MeOH was added to the oily residue to give 4-amino-3-cyano-3,5-bis(2-pyridyl)-3H-pyrazole (2)[8] in 21% yield (Scheme 1). The structure was confirmed on the basis of the amino and cyano absorptions in the IR spectrum and of a singlet at δ 77.2 assigned to the quarternary sp^3 carbon in addition to five singlets and eight doublets of sp^2 and sp carbons in the ^{13}C-NMR spectrum. In contrast to 1a, treatment of 3,6-bis(4-pyridyl)-1,2,4,5-tetrazine (1b) in a similar manner resulted, unexpectedly, in the incorporation of toluene to give 4-amino-1-benzyl-3,5-bis(4-pyridyl)-1H-pyrazole (3a)[9] in 44% yield. The IR and ^{13}C-NMR spectra of 3a showed the absence of both cyano groups and the quarternary sp^3 carbons. Instead, the presence of a methylene group was proved by a singlet at δ 5.25 and a triplet at δ 54.4 in the ^{1}H- and ^{13}C-NMR spectra, respectively. Moreover, the remaining six singlets and seven doublets in the sp^2 carbon region in the ^{13}C-NMR spectrum were compatible only with the structure 3a. The reaction of 1b with TMSCN in refluxing o-, m-, or p-xylene incorporated similarly the solvent to afford 3b-d[9] in 44-55% yields. On the other hand, the reaction of 3,6-bis(methoxycarbonyl)-1,2,4,5-tetrazine (1c) in toluene or xylenes yielded 4-amino-3,5-bis(methoxycarbonyl)-1H-pyrazole (4)[10] as the major product (21-35 %), accompanied by the minor products 3e-h[11] (4-17%), after column chromatography on silica gel with $CHCl_3$. The ^{13}C-NMR spectra of 3g and 3h showed three singlets of sp^2 carbons at δ 136.7-140.1 assignable to the ring carbons of the pyrazole nucleus in the same pattern as observed in the case of

Scheme 2



3a, 3b, and 4. 3,6-Diphenyl-1,2,4,5-tetrazine gave only intractable materials.

The plausible mechanism for the formation of 2, 3, and 4 may be described as shown in Scheme 2. The initial formation of the TMSCN adduct 5 is in accord with the general trend of 1,2,4,5-tetrazines.[12] Its intramolecular cyclization to 6 (path a) followed by attack of TMSCN (path c), or its ring opening to 7 by attack of TMSCN (path b)[13] followed by cyclization could yield 3H-pyrazole 8. The product 2 would be formed directly from 8 (R=2-pyridyl), whereas, in the case of 1b and 1c, 8 (R=4-pyridyl, CO_2Me) would extrude CN^- and incorporate toluene or xylene, resulting in the formation of aromatic 1H-pyrazoles 3. The discrete formation of 2 and 3 from 8 could be attributable to the difference in the electron-attractive ability between 2- and 4-pyridyl groups. Thus, more electron-attractive 2-pyridyl group[14] would retard the elimination of CN^- from 8, giving 2. On the other hand, it would be presumed that 4 is derived from 9 by hydrogen abstraction from the surroundings, although details of this process remain equivocal at present.

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8. 2: Mp 204-205°C; MS m/z 262 (M^+); IR (KBr) 3550, 3420, 3100, 2200 cm^{-1}; ^1H-NMR (DMSO-d_6) δ 6.97-9.17 (m, 8H), 10.65 (br s); ^{13}C-NMR (DMSO-d_6) δ 77.2 (s), 116.6 (d), 118.7 (d), 119.1 (d), 119.5 (d), 121.0 (s), 126.1 (d), 127.7 (d), 131.5 (s), 132.7 (s), 137.2 (d), 147.2 (d), 152.9 (s), 156.1 (s).

9. 3a: Mp 179-181°C; MS m/z 327 (M^+); IR (KBr) 3350, 3200, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.23 (br s, 2H), 5.25 (s, 2H), 6.83-8.68 (m, 13H); ^{13}C-NMR ($CDCl_3$) δ 54.4 (t), 120.8 (d), 123.5 (d), 126.8 (d), 127.2 (s), 127.9 (d), 128.8 (d), 129.0 (s), 136.8 (s), 137.1 (s), 137.9 (s), 140.7 (s), 150.3 (d), 150.8 (d). 3b: Mp 142-145°C; MS m/z 341 (M^+); IR (KBr) 3310, 3200, 1595 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.20 (s, 3H), 3.32 (br s, 2H), 5.30 (s, 2H), 6.68-8.72 (m, 12H); ^{13}C-NMR ($CDCl_3$) δ 19.0 (q), 52.2 (t), 120.7 (d), 123.3 (d), 126.4 (d), 126.5 (d), 127.1 (s), 127.8 (d), 129.2 (s), 130.4 (d), 134.8 (s), 135.2 (s), 137.1 (s), 137.8 (s), 140.7 (s), 150.2 (d), 150.7 (d). 3c: Mp 156-158°C; MS m/z 341 (M^+); IR (KBr) 3500, 3300, 3200, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.28 (s, 3H), 3.48 (br s), 5.28 (s, 2H), 6.88 -8.75 (m, 12H). 3d: Mp 208-210°C; MS m/z 341 (M^+); IR (KBr) 3340, 3200, 1595 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.31 (s, 3H), 3.07 (br s, 2H), 5.29 (s, 2H), 6.86-8.76 (m, 12H).

10. 4: Mp 186-188°C; MS m/z 199 (M^+); IR (KBr) 3500, 3380, 3230, 1695, 1675, 1600 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 3.81 (s, 6H), 5.43 (br s, 2H), 13.70 (br s, 1H); ^{13}C-NMR (DMSO-d_6) δ 51.1 (q), 51.2 (q), 116.6 (s), 128.5 (s), 139.2 (s), 159.8 (s), 163.1 (s).

11. 3e: Mp 121-123°C; MS m/z 289 (M^+); IR (KBr) 3320, 3170, 1705, 1680 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.89 (s, 6H), 4.76 (s, 2H), 6.14 (br s), 7.29 (s, 5H). 3f: Mp 136-138°C; MS m/z 303 (M^+); IR (KBr) 3360, 3180, 1685 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.37 (s, 3H), 3.89 (s, 6H), 4.73 (s, 2H), 7.22 (s, 4H). 3g : Mp 101-103°C; MS m/z 303 (M^+); IR (KBr) 3350, 3230, 1700 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.34 (s, 3H), 3.90 (s, 6H), 4.73 (s, 2H), 7.12 (s, 4H); ^{13}C-NMR ($CDCl_3$) δ 21.4 (q), 50.8 (t), 51.8 (q), 124.5 (d), 127.9 (d), 128.3 (d), 128.4 (s), 138.1 (s), 139.7 (s), 140.1 (s), 161.6 (br s). 3h: Mp 145-147 °C; MS m/z 303 (M^+); IR (KBr) 3360, 3150, 1715, 1685 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.32 (s, 3H), 3.89 (s, 6H), 4.74 (s, 2H), 6.08 (br s), 7.15 (s, 4H); ^{13}C-NMR ($CDCl_3$) δ 21.1 (q), 50.5 (t), 51.8 (q), 127.4 (d), 129.2 (d), 136.7 (s), 136.8 (s), 140.1 (s), 161.6 (s), 161.7 (s).

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