The Reaction of 1,2,3-Triazines with Grignard Reagents

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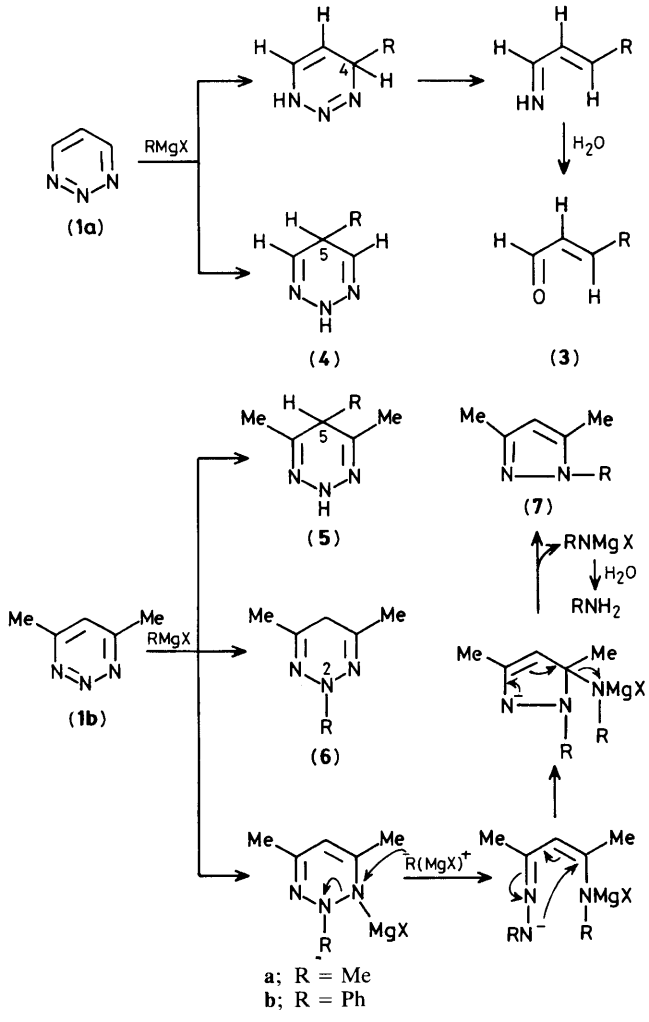
Monocyclic 1,2,3-triazines reacted with Grignard reagents to form adducts due to N-2 and C-5 attack together with β-substituted acrylaldehydes and *N*-substituted pyrazoles; the results show that the N-2, C-4, and C-5 positions are reactive towards Grignard reagents.

The behaviour of 1,2,3-triazines (**1a**) and (**1b**) towards Grignard reagents is noteworthy owing to their π-deficient character. With regard to this, the reactions of 4-substituted 1,2,3-benzotriazines (**2**) with alkyl Grignard reagents were demonstrated by Storr *et al.*[1] and it was found that attack by the reagents occurs at N-2. The reaction sites of (**2**), however, are quite restricted and the reactivity of the triazine ring might be influenced to some extent by the fused benzo moiety. This paper describes the reaction of monocyclic 1,2,3-triazines (**1a**) and (**1b**) with Grignard reagents.

1,2,3-Triazine (**1a**)[2] was treated with 1 equiv. MeMgI (in Et_2O, at 0 °C → room temp. for 0.5 h) and then quenched with aq. NH_4Cl. The v.p.c.–mass spectrum of the ethereal layer† showed the presence of a reasonable amount of crotonaldehyde (**3a**),‡ but the major product was the symmetrical adduct, 5-methyl-2,5-dihydro-1,2,3-triazine (**4a**), (42%

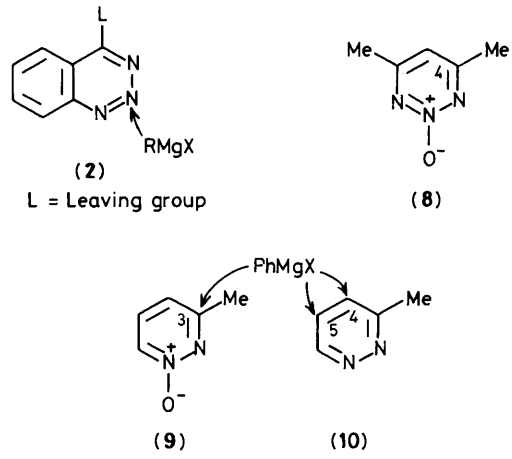
† Ionization of the molecule was carried out at 70 eV; *m/z* 70, 100%; 69, 48%; 41, 87%; 39, 55%.

‡ Isolation of crotonaldehyde has not been accomplished.



Scheme 1

yield).§ Treatment of (**1a**) with PhMgBr under similar conditions and work-up gave cinnamaldehyde (**3b**) (52%) and the 2,5-adduct (**4b**) (13%).§



The formation of aldehydes (**3**) is the result of nucleophilic attack by the Grignard reagent at C-4 of the triazine (**1a**), and thus reveals that C-4 and C-5 of the triazine are reactive towards Grignard reagents.

In the case of triazine (**1b**),[3] where both C-4 and C-6 are blocked with methyl groups, the reaction with MeMgI afforded the symmetrical adducts, 4,5,6-trimethyl-2,5-dihydro-1,2,3-triazine (**5a**) (20%)§ and 2,4,6-trimethyl-2,5-dihydro-1,2,3-triazine (**6a**) (25%),§ and *ca.* 10% of 1,3,5-trimethylpyrazole (**7a**). The reaction of (**1b**) with PhMgBr gave compound (**5b**) (6%),§ the dihydro compound (**6b**) (37%),§ and the pyrazole (**7b**) (10%). In addition, the presence of aniline in the reaction mixture was confirmed by v.p.c.

Of the products from (**1b**), the compounds (**5**) and (**6**) are the products caused by C-5 attack and N-2 attack, respectively, and the formation of compounds (**7**) might proceed *via* a sequence which involves attack at N-2 as shown in Scheme 1.¶

Thus, the data show that not only N-2 but also C-4 and C-5 of the 1,2,3-triazines are reactive towards Grignard reagents and this appears to be the first isolation of adducts owing to N-2 and C-5 attack on the 1,2,3-triazines by Grignard reagents.

Additionally, treatment of 4,6-dimethyl-1,2,3-triazine 2-oxide (**8**)[3]‖ with the Grignard reagents under the conditions described resulted in almost complete recovery of the starting material, a rather unexpected result because C-3 of 3-methylpyridazine 1-oxide (**9**),[4] which is positionally comparable with C-4 of compound (**8**), is reactive with PhMgBr under similar conditions, as are C-4 and C-5 of 3-methylpyridazine (**10**).[5]

Received, 28th May 1985; Com. 735

References

1 J. J. A. Campbell, S. J. Noyce, and R. C. Storr, *J. Chem. Soc., Chem. Commun.*, 1983, 1344.
2 A. Ohsawa, H. Arai, H. Ohnishi, and H. Igeta, *J. Chem. Soc., Chem. Commun.*, 1981, 1174.
3 A. Ohsawa, H. Arai, H. Ohnishi, and H. Igeta, *J. Chem. Soc., Chem. Commun.*, 1980, 1182.
4 H. Igeta, T. Tsuchiya, and T. Nakai, *Tetrahedron Lett.*, 1969, 2667.
5 I. Crossland and H. Kofod, *Acta Chem. Scand.*, 1970, **24**, 751; R. L. Letsinger and R. Lasco, *J. Org. Chem.*, 1956, **21**, 812.

§ Compound (**4a**), colourless flakes (hexane–Et_2O), m.p. 53—55 °C, ^{1}H n.m.r. ($CDCl_3$) δ (*vs.* $SiMe_4$):1.32(3H, d, *J* 6.7 Hz, $CHCH_3$), 2.16(1H, q, *J* 6.7 Hz, $CHCH_3$), 6.50(2H, s, N=C*H* × 2), 8.80 (1H, br. s, N*H*); ^{13}C n.m.r. ($CDCl_3$) δ (*vs.* $SiMe_4$): 13.45 (CH_3), 27.39 ($CHCH_3$), 139.98 (N=*C*H). (**4b**), colourless needles (hexane–Et_2O), m.p. 94—97 °C, ^{1}H n.m.r. δ: 3.18 (1H, br. d, *J* 1.5 Hz, C*H*Ph), 6.61 (2H, d, *J* 1.5 Hz, N=C*H* × 2), 7.10—50 (5H, m, phenyl), 8.82 (1H, br. s, N*H*); ^{13}C n.m.r. δ: 39.03 (*C*HPh), 127.72, 128.28, 129.06 (phenyl carbons), 133.18 (N=*C*H), 137.83 (phenyl 1-C). The adduct (**5a**) was identical with the compound which was obtained from 4,5,6-trimethyl-1,2,3-triazine by catalytic hydrogenation (Pd-C) or $NaBH_4$ reduction in MeOH; colourless needles, (pentane–Et_2O), m.p. 52—54 °C, ^{1}H n.m.r. δ: 1.02 (3H, d, *J* 6.6 Hz, $CHCH_3$), 2.00 (6H, s, N=C–CH_3 × 2), 2.67 (1H, q, *J* 6.6 Hz, $CHCH_3$), 8.45 (1H, br. s, N*H*). Compound (**6a**) was authentically obtained from $NaBH_4$ reduction (in MeOH) of 2,4,6-trimethyl-1,2,3-triazinium iodide; colourless oil, ^{1}H n.m.r. δ: 2.00 (6H, s, N=C–CH_3 × 2), 2.38 (2H, s, CH_2), 3.30 (3H, s, NCH_3). (**5b**), colourless prisms (Et_2O), m.p. 109—111 °C, ^{1}H n.m.r. δ: 1.95 (6H, s, N=C–CH_3 × 2), 3.75 (1H, s, C*H*Ph), 6.90—7.22 (5H, m, phenyl), 8.08 (1H, br. s, N*H*); ^{13}C n.m.r. δ: 20.76 (CH_3), 44.35 (*C*HPh), 127.45, 128.03, 128.91 (phenyl carbons), 137.12 (phenyl 1-C), 141.17 (N=*C*–CH_3). (**6b**) pale yellowish prisms (Et_2O), m.p. 51—52 °C, ^{1}H n.m.r. δ: 2.09 (6H, s, N=C–CH_3 × 2), 2.59 (2H, s, CH_2), 6.78—7.60 (5H, m, phenyl); ^{13}C n.m.r. δ: 21.90 (CH_3), 29.90 (CH_2), 115.54 (phenyl 3-C), 121.87 (phenyl 4-C), 128.55 (phenyl 2-C), 139.88 (phenyl 1-C), 147.52 (N=*C*–CH_3).

¶ Treating (**6a**) with MeMgI under the described conditions did not give (**7**); it resulted in essentially complete recovery of (**6**).

‖ Details of nucleophilic reactions on the triazine *N*-oxides will appear later.