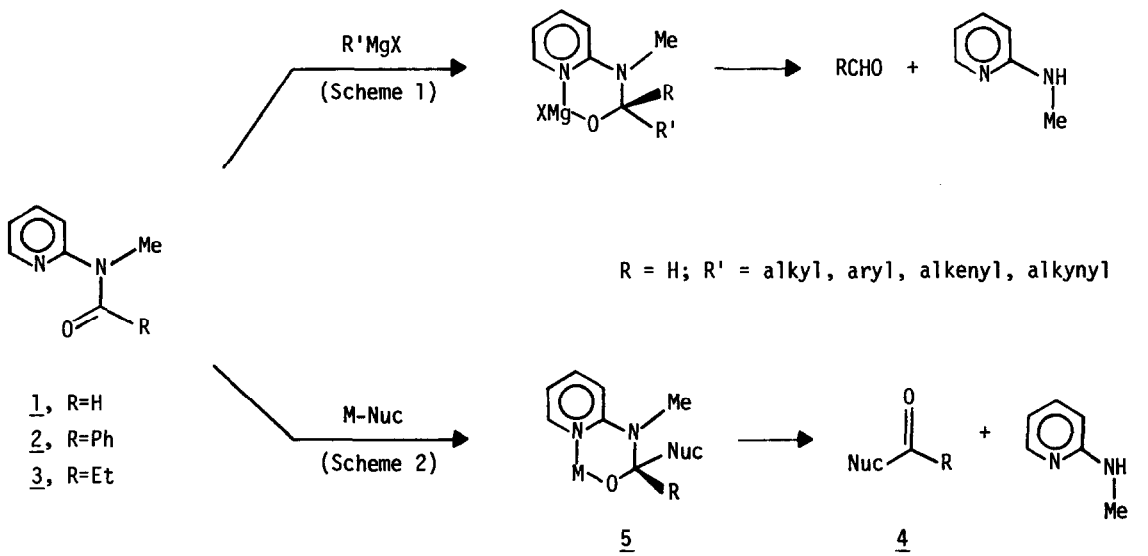
Tetrahedron Letters No. 52, pp 5179 - 5182.

0040-4039/78/1222-5179$02.00/0

N-METHYLAMINO PYRIDYL AMIDES (MAPA) II. AN EFFICIENT ACYLATING AGENT FOR VARIOUS NUCLEOPHILES AND SEQUENTIAL ADDITION TO UNSYMMETRICAL tert-ALCOHOLS.

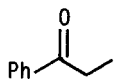
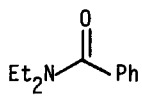
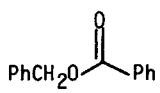
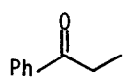
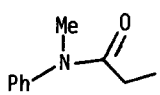
A. I. Meyers* and Daniel L. Comins
Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

We recently described the utility of 1 as an efficient formylating agent for Grignard reagents (Scheme 1). The presence of the pyridyl nitrogen atom was assumed to provide a strong bidentate for magnesium which facilitated carbanion transfer to the formyl group leading to aldehydes.[1] We



now report that N-methylamino pyridine amides (MAPA) 2, 3 react rapidly and efficiently with a variety of metallo-nucleophiles (M-Nuc) at 0° or below furnishing acyl derivatives, 4 (Table 1). As seen from the table, lithium aluminum hydride gave benzyl alcohol when treated with 2 whereas $NaAl(OCH_2CH_2OMe)_2(NC_2H_4NMe)H$[2] led to a good yield of benzaldehyde. This behavior suggested that lithium coordination in 5 rendered the C-N bond labile to further attack by hydride ion thus producing the alcohol. Furthermore, addition of 1.0 equiv n-BuLi to 2 or 3 gave mixtures of ketones and tertiary alcohols at all temperatures from -78 to 0°. This is contrasted to the addition of

TABLE 1 Acylation of Nucleophiles with MAPA

MAPA	Nucleophile	Conditions	Products, 4	% Yield [a]
2	EtMgBr	THF, -78°		83
2	$NaAl(OCH_2CH_2OMe)_2H$ NC_2H_4NMe	THF, 0°	PhCHO	77
2	$LiAlH_4$	THF, 0°	$PhCH_2OH$	98
2	Et_2NMgCl	THF, -23°		94
2	$PhCH_2ONa$	THF, 0°		75
3	PhMgCl	THF, -78°		75
3	PhN(Me)MgCl	THF, 0°		89

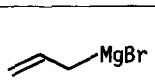
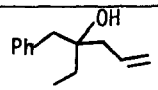
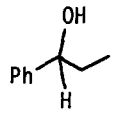
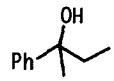
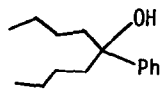
a) Yields represent purified products (preparative layer or medium pressure liquid chromatography). All products had identical spectral and physical properties with authentic samples

Grignard reagents to 2 and 3 which led to ketones in good yield. Mukaiyama[3] has previously reported a similar use of 2-(thioacyl)pyridines and others have described various reagents for acylation.[4] The MAPA reagent appears to be quite general for the formation of aldehydes, ketones, alcohols, amides, and esters as seen from the high yields given in the table.

The previous observation that 5 (M=Li) is sensitive to further alkylation suggested that sequential introduction of different nucleophiles may be feasible. Addition of 1.0 equiv of Grignard (-70°) followed by 1.0 equiv of a second nucleophile afforded the tert-alcohols (Table 2, Scheme 3). Thus, a "one-pot" synthesis of unsymmetrical 3° and 2° alcohols appears to be viable using the MAPA reagents. Application of this methodology to macrocyclic syntheses is presently in progress. Some typical experimental details are given below:

N-(Methylaminopyridine)benzamide 2 - A solution of n-butyllthium (93 mmoles in hexane) was added to N-methylamino pyridine (93 mmoles in 50 ml THF) at -78° and stirred for 30 min. This yellow solution was added dropwise (20 min) to benzoyl chloride (95 mmoles in 100 ml THF) at -78°, stirred for 15 min, and warmed to ambient. Water (25 ml) and ether (25 ml) were added, followed

TABLE 2 Sequential Introduction of Nucleophiles to MAPA (Scheme 3)

MAPA	First (MN^1) Nucleophile	Second (MN^2) Nucleophile	Product	% Yield (after PLC)
3	$PhCH_2MgCl$ (-78°)			95
3	PhMgCl (-78°)	$LiAlH_4$		70
3	PhMgCl (-78°)	CH_3MgCl		70
2	n-BuLi (-78°)	n-BuLi		98

by ether extraction, drying and concentration to give an oil. Distillation (118°-123° at 0.08 torr) furnished 17.2 g (85%) of 2.[5]

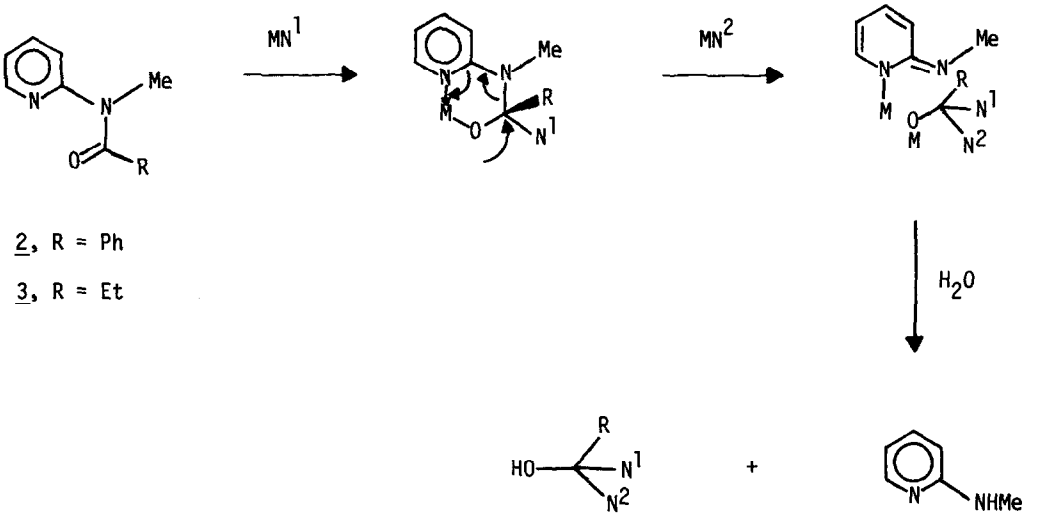
N-(Methylaminopyridine)propionamide 3 - A mixture of 2-(N-methylamino)pyridine (0.1 mole)[1] and propionic anhydride (20 ml) were heated at reflux for 17 h. Excess anhydride was removed by distillation (10 torr) and the residue distilled, bp 74-80° (0.08 torr) to give 15 g (91%) 3; ir (film) 1670 cm^{-1}, nmr (CCl_4) δ 1.08 (t, 3), 2.32 (q, 4), 3.31 (s, 3), 6.95-7.92 (m, 3).

Procedure for Acylation of 2, 3 - A solution of 2 or 3 (3 mmoles in 10 ml THF) cooled to the temperature indicated in Table 1 is treated dropwise with 1.2 equiv of the appropriate nucleophile. The reaction mixture was stirred at the indicated temperature until complete by tlc (acetone-hexane), usually less than 2 h. Aqueous HCl (5%, 25 ml) was added slowly followed by ether extraction (3 X 25 ml). The organic phase was washed with brine, dried (K_2CO_3) and concentrated to give the product, purified by preparative layer chromatography (acetone-hexane silica gel. The N-methylamino pyridine may be recovered from the aqueous phase by neutralization with bicarbonate.

Procedure for sec- and tert-Alcohols - The above procedure was followed for the addition of the first nucleophile (1.0 equiv) at the temperature indicated in Table 2. After 15 min, the second nucleophile (1.3 equiv) was added and the cooling bath removed. The reaction stirred at ambient until tlc indicated completion. Isolation and purification was the same as described above.

ACKNOWLEDGEMENT Financial assistance for this work was provided by the National Institutes of Health.

Scheme 3



2, R = Ph

3, R = Et

REFERENCES

1. D. Comins and A. I. Meyers, Synthesis, 403 (1978).

2. T. Tokoroyama and R. Kanazawa, Synthesis, 526 (1976).

3. T. Mukaiyama, M. Araki, and T. Takei, J. Am. Chem. Soc., 95, 4763 (1973).

4. A survey of these methods is given in an excellent review; S. Masamune, G. S. Bates, and J. W. Corcoran, Angew. Chem. Int. Ed., 16, 585 (1977).

5. A. E. Tschitschibabin, I. L. Knunjanz, Ber., 61B, 2215 (1928).

(Received in USA 7 August 1978)