RING CONSTRUCTION OF SEVERAL HETEROCYCLES WITH PHOSPHORUS PENTOXIDE-METHANESULFONIC ACID (PPMA)

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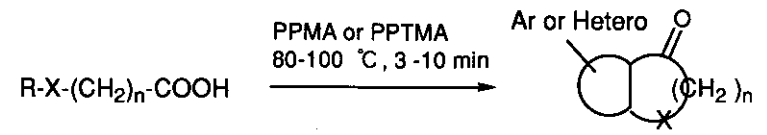
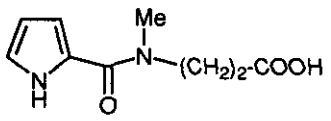
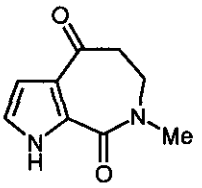
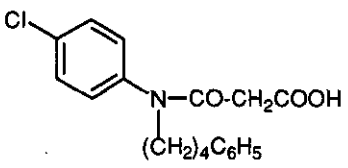
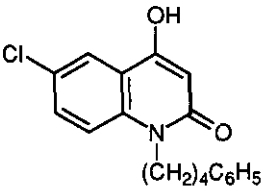
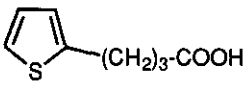
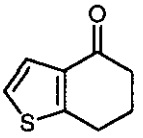
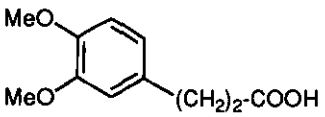
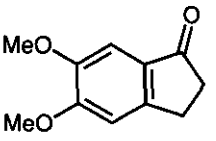
Abstract- The cyclization reactions with CH_3SO_3H/P_2O_5 (PPMA) or CF_3SO_3H/P_2O_5 (PPTMA) at 80-100 ° C for 3-10 min afforded several heterocycles (6, 7-dihydropyrrolo[2, 3-c]azepin-4, 8(1H, 5H)-dione, 4-oxo-4, 5, 6, 7-tetrahydrothianaphthene, carbostyril derivatives).

On the research of developments for more effective cyclization procedures for pyrroloazepine, thianaphthene, and carbostyril derivatives, we found that the cyclization with phosphorus pentoxide and methanesulfonic acid (PPMA; 1:9 weight ratio) provided those heterocyclic compounds in good yield. Distinctly, this procedure is more efficient and convenient than polyphosphoric acid (PPA) method, since it is very troublesome to handle with PPA because of viscousness. Moreover, 10-30 weight ratio of PPA to a substrate is usually required. Although PPMA was used for peptide condensations,[1] the application for cyclization reaction has not been studied enough to date.[2, 3] The reagent could be prepared at 80-100° C within 10-30 min. The resulted solution was employed *in situ* for the cyclization reaction (PPMA: substrate = 10 : 1.5-2.0 weight ratio). Generally, the reactions proceeded very quickly (for 3-10 min) at 80-100 ° C to give the products in high yields. (See Table) Therefore, compound (2) was obtained without any by-product, and compound (4) was given without decarboxylation

Table. Facile Ring Construction of Arylalkylcarboxylic Acid with PPMA and PPTMA



X=CH_2, $CONR^1$, NR^2CO
n=1,2

Substrate	Reagent	Temp. (℃)	Time (min)	Product	Yield (%)
 1	PPMA	100	3	 2	85
	PPMA	90	5		90
	PPMA	80	10		90
	PPTMA	90	5		71
	PPA	100	30		80
 3	PPMA	80	10	 4	91
 5	PPMA	100	5	 6	76
 7	PPMA	100	3	 8	95
	PPA	65	25		90

although decarboxylation of 3 was often accompanied under other acidic conditions. Usually, crystalline powder of a carboxylic acid was added directly to PPMA. But, an oily compound may be dissolved in methanesulfonic acid and added as a hot solution (80-100° C). PPMA has a merit that it could be employed even on an industrial large-scale preparation since it handled easily because of a liquid.

Thus, novel 7-methyl-6,7-dihydropyrrolo[2,3-c]azepin-4,8(1H, 5H)-dione (2) was obtained by the facile cyclization of 3-(N-methyl-2-pyrrolecarboxamide)propionic acid (1)[4] with PPMA in 90 % yield. Subsequently, 6-chloro-N-(4-chlorophenyl)-4-hydroxyquinolin-2(1H)-one (4) (carbostyril), 4-oxo-4,5,6,7-tetrahydrothianaphthene (6), and 5,6-dimethoxyindan-1-one (8) were given by the cyclization of [N-(4-chlorophenyl)-N-(4-phenylbutyl)aminocarbonyl]acetic acid (3), 4-(2-thienyl)butanoic acid (5), and 3-(3,4-dimethoxyphenyl)propionic acid (7) with PPMA, respectively. Apparently, the completion of reactions depended upon the reaction temperatures and times, such as at 100 ° C within 3 min, at 90 ° C within 5 min, or 80 ° C within 10 min. Similarly, we prepared PPTMA from phosphorus pentoxide and trifluoromethanesulfonic acid (1:9 weight ratio). PPTMA was found to be extremely powerful for the cyclization and to be sensitive to a moisture. Thus, the cyclization reaction of compound (1) with PPTMA occurred at 90° C for 5 min to afford (2).

Consequently, these procedures should be applied to other syntheses of bicyclic heterocycles and aromatic compounds.

EXPERIMENTAL

Melting points were determined with Yanagimoto (Yanako) micro-melting point apparatus HK-10D and are uncorrected. ^{1}H-Nmr spectra (ppm, δ) were recorded with a JEOL JNMA 300 (300 MHz) spectrometer with tetramethylsilane as an internal standard. Ir spectra (cm^{-1}) were taken on a PERKIN ELMER FT 1650 infrared spectrophotometer. Mass spectra were taken on Finigan TSQ 700. Column chromatography was performed on Merck silica gel (70-230 mesh).

Synthesis of 7-methyl-6,7-dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione (2)

i) PPMA method[4]: Phosphorous pentoxide (540 mg, 3.8 mmol) was added to methanesulfonic acid (5.46 g, 56.9 mmol) and the mixture was vigorously stirred at 80° C for 30 min. To a stirred

colorless solution was added 3-(N-methyl-2-pyrrolecarboxamide)propionic acid (1)[4] (1.0 g, 5.1 mmol) (as crystalline powder) at 80 ° C. The solution was stirred at the same temperature for 10 min and poured into ice-water (No exothermic reaction occurred.). The solution was extracted with $CHCl_3$ three times and the organic layer was washed with 0.5 % aq. $NaHCO_3$ solution, dried over anhyd. $MgSO_4$, and evaporated to leave the solid, which was crystallized from $CHCl_3$-AcOEt to give pyrroloazepine derivative (2) (817 mg, 90 %).

ii) PPTMA method[4]: Phosphorous pentoxide(100 mg, 0.70 mmol) was added to trifluoromethanesulfonic acid (900 mg, 6.0 mmol) at 0 ° C. The mixture was vigorously stirred at 90 ° C for 5 min. To a stirred colorless solution was added 3-(N-methyl-2-pyrrolecarboxamide)propionic acid (1) (167 mg, 0.85 mmol) (as crystalline powder) at 90° C. After 3 min, the reaction mixture was poured into ice-water and extracted with $CHCl_3$. The organic layer was washed with 0.5 % aq. $NaHCO_3$ solution, dried over anhyd. $MgSO_4$, and evaporated to leave the solid, which was crystallized from $CHCl_3$-AcOEt to give compound (2) (108 mg, 71 %). mp 175-177 ° C (colorless needles). Ir ($CHCl_3$, cm^{-1}): 3425, 1665, 1620. ^{1}H-Nmr (δ ppm, $CDCl_3$) 2.89 (2H, m), 3.26 (3H, s), 3.72 (2H, m), 6.78, (1H, br d, J=2.9 Hz), 6.94 (1H, br d, J=2.9 Hz), 10.50 (1H, br s). Ms(FAB, m/z)=179 (M^+ +1). Anal. Calcd for $C_9H_{10}N_2O_2$:C, 60.66; H, 5.66; N, 15.72. Found:C, 60.61; H, 5.76; N, 15.66.

Synthesis of 6-chloro-N-(4-chlorophenyl)-4-hydroxyquinolin-2-(1H)-one (4)

Phosphorus pentoxide (250 mg, 1.76 mmol) was added to methanesulfonic acid (MSA) (2.5 g, 26 mmol). After stirring at 80 ° C for 25 min, a hot solution of 3 (520 mg, 1.50 mmol) in MSA (2.0 g, 20.8 mmol) was added. Stirring was continued at the temperature for 10 min. The reaction mixture was poured into ice-water and extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhyd. $MgSO_4$ and evaporated to leave the residue, which was purified with SiO_2 short column chromatography ($CHCl_3$) to give oily compound (4) (445 mg, 91 %). ^{1}H-Nmr (δ, $CDCl_3$) 1.55-1.75 (4H, m), 2.58-2.68 (2H, m), 4.10-4.25 (2H, m), 5.90 (1H, s), 7.10-7.30 (5H, m), 7.44 (1H, d, J=9 Hz), 7.56 (1H, dd, J=9, 3 Hz), 7.83 (1H, d, J=3 Hz), 11.35-11.52 (1H, br s). Ms(FAB, m/z)=328 ($M^•$ +1). Anal. Calcd for $C_{19}H_{18}NO_2Cl$:C, 69.62; H, 5.54; N, 4.27. Found:C, 69.60; H, 5.64; N, 4.31.

Synthesis of 4-oxo-4,5,6,7-tetrahydrothianaphthene (6)

Similarly, PPMA was prepared from phosphorus pentoxide (600 mg, 4.23 mmol) and MSA (6.0 g, 62.5 mmol) at 100 ° C and the compound (5) (1.0 g, 5.88 mmol) was added all at once. After stirring at 100 ° C for 5 min, the reaction mixture was worked-up in a same manner. The residue was purified with SiO_2 column chromatography ($CHCl_3$) to give compound (6) (678 mg, 76 %) as pale yellow crystals. mp 38-40 ° C. Ir (KBr, cm^{-1}) 1669. ^{1}H-Nmr (δ, $CDCl_3$) 2.23 (2H, m), 2.56 (2H, t, J=6.0 Hz), 3.04 (2H, t, J=6.0 Hz), 7.06 (1H, d, J=5.1 Hz), 7.39 (1H, d, J=5.1 Hz). Ms(FAB, m/z)=153 (M^+ +1). Anal. Calcd for C_8H_8SO:C, 63.13; H, 5.30. Found :C, 63.30; H, 5.28.

Synthesis of 5,6-dimethoxyindan-1-one (8)

PPMA was prepared in a same manner, and 3-(3,4-dimethoxyphenyl)propionic acid (7) (1.0 g, 4.76 mmol) was added all at once at 100° C. After stirring for 3 min, the reaction mixture was worked-up to leave the solid, which was crystallized from acetone-n-hexane to afford compound (8) (868 mg, 95 %). mp 118-120 ° C. Ir (KBr, cm^{-1}) 1702. ^{1}H-Nmr (δ, $CDCl_3$) 2.60 (2H, m), 2.98 (2H, t, J=6.0 Hz), 3.84 (3H, s), 3.90 (3H, s), 6.83 (1H, s), 7.11 (1H, s). Ms(FAB, m/z)=193 (M^+ +1). Anal. Calcd for $C_{11}H_{12}O_3$:C, 68.74; H, 6.29. Found :C, 68.89; H, 6.16.

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REFERENCES AND NOTES

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3. R. L. Cargill and T. E. Jackson, *J. Org. Chem.*, 1973, 38, 2125.
4. H. Cho, A. Mizuno, M. Hamaguchi, and T. Tatsuoka, *Japan Patent Kokai*, 1993, H5-25128 (*Chem. Abstr.*, 1993, 119, 95364). [Application; 1990, H2-119995; 1991, H3-108166].
5. P. E. Eaton and R. H. Mueller, *J. Am. Chem. Soc.*, 1972, 94, 1014.
6. In literatures 2 and 5, the chemical structure of PPMA is ambiguously mentioned. They noted that it might be a mixture of methanesulfonic acid and methanesulfonic anhydride, but described that both reagents mixed did not effect the conversion satisfactory.

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