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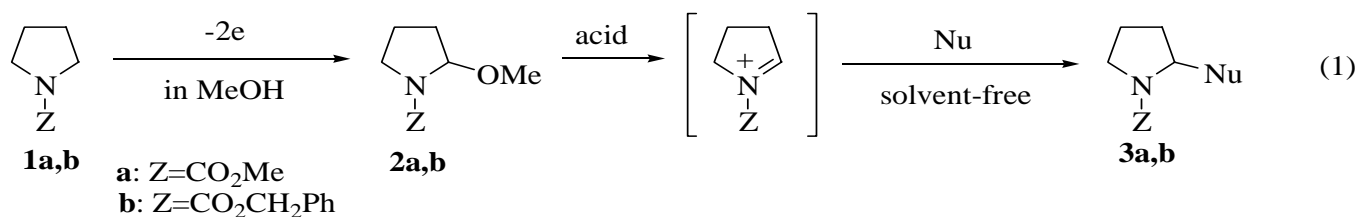
THE MANNICH-TYPE REACTION BETWEEN *N,O*-ACETALS AND CARBON NUCLEOPHILES UNDER SOLVENT-FREE CONDITIONS

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Abstract—The Mannich-type reaction for 1-methoxycarbonyl- or 1-benzyloxy-carbonyl-2-methoxypyrrolidine with carbon nucleophiles such as acetylacetone, methyl acetoacetate, dimethyl malonates, benzoylacetone, dibenzoylmethane, or cyclohexane-1, 3-dione proceeded by acid catalysis under solvent-free conditions with more efficiency than that in dichloromethane.

The Mannich-type reactions between *N*-acyliminium ions generated from *N,O*-acetals and nucleophiles have been frequently utilized to introduce substituents at the α -position of various amines.^{1,2} We have already exploited some reactions between *N,O*-acetals prepared by electrochemical oxidation³ and various nucleophiles to afford some important α -substituted amines.⁴ Those reactions were carried out in large volume of organic solvents which seemed to be environmentally unsuitable and uneconomical.⁵ So we examined solvent-free⁶ processes for such reactions, and found that the Mannich-type reaction for *N,O*-acetals (**2a,b**) proceeded through acyliminium ions under solvent-free conditions more efficiently than ones in organic solvents (Eq. 1). We report herein the detail of the results and the comparison with the corresponding reactions carried out using organic solvents.



The preparation of **2a,b** was easily achieved by electrochemical oxidation of 1-methoxycarbonyl- or benzyloxycarbonylpyrrolidines (**1a,b**) in methanol.² With **2a,b** in hand, we first examined the reactions of **2a** with liquid active methylene compounds (**4p-q**) (3 equiv. to **2a**),⁷⁻⁹ a kind of carbon nucleophiles, in the presence of a catalytic amount of some acids under solvent-free¹⁰ and solvent (CH₂Cl₂) conditions to afford the products (**3ap-ar**)⁷ (Eq. 2). The results are summarized in Table 1 which shows the yields based on **2a**. The yields depended on the reaction conditions, that is, the yields of the coupling product (**3ap**)¹¹ in the case using acetylacetone (**4p**) under solvent-free conditions were much higher than under solvent conditions (entries 1-4), and the yields of **3aq** and **3ar** in the cases using acetoacetate (**4q**) and dimethyl malonate (**4r**) under solvent-free conditions were similar to or better than under solvent conditions.^{12,13}

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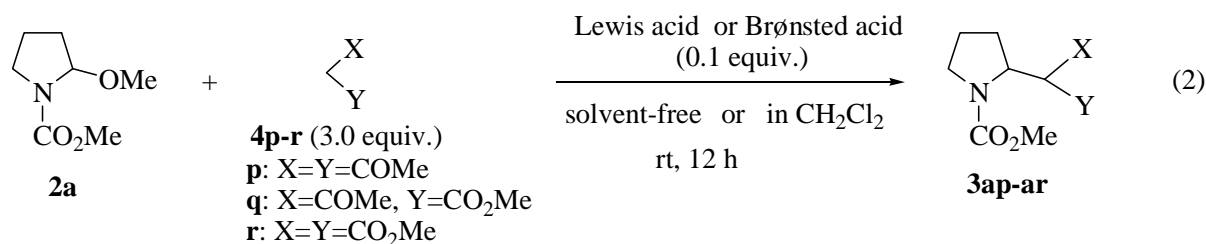
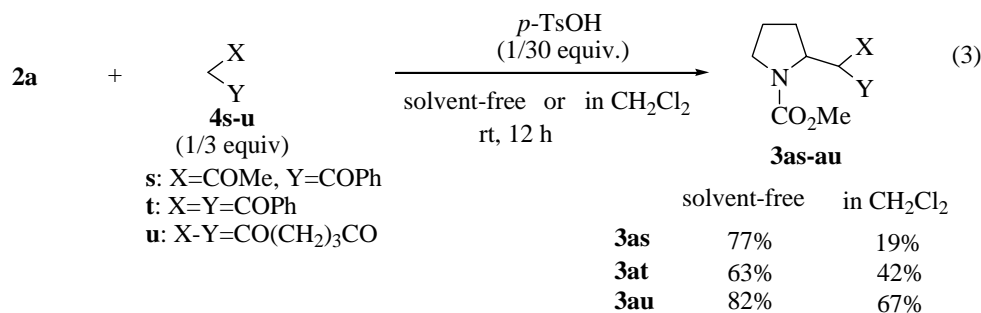


Table 1. Solvent-free and solvent reaction of *N,O*-acetal (**2a**) with active methylene compounds (**4p-r**) in the presence of acid

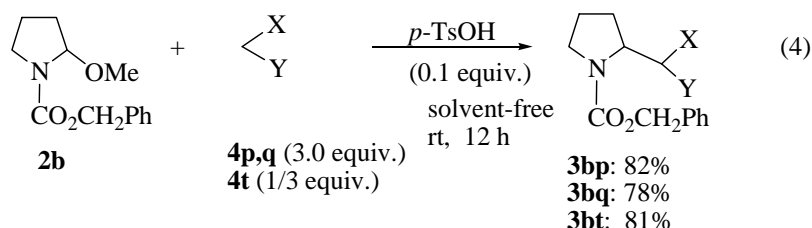
entry	nucleophile	acid ^a	product	yield (%)	
				solvent-free	in CH ₂ Cl ₂
1	4p	TiCl ₄	3ap	89	70
2	4p	TiCl ₂ (<i>O-i</i> -Pr) ₂	3ap	84	16 ^d
3	4p	CF ₃ SO ₃ H	3ap	77	44
4	4p	<i>p</i> -TsOH	3ap	94	67
5	4q	TiCl ₄	3aq^c	93	87
6	4q	TiCl ₂ (<i>O-i</i> -Pr) ₂	3aq^c	87	94
7	4q	CF ₃ SO ₃ H	3aq^c	93	56
8	4q	<i>p</i> -TsOH	3aq^c	74	61
9	4r	TiCl ₄ ^b	3ar	76	80
10	4r	TiCl ₂ (<i>O-i</i> -Pr) ₂	3ar	61	57
11	4r	<i>p</i> -TsOH	3ar	trace ^d	trace ^d

^a 0.1 equiv. ^b Et₃N (0.1 equiv.) was added. ^c The ratio of diastereomer for product (**3aq**) was about 2:1. ^d Conversions were very low.

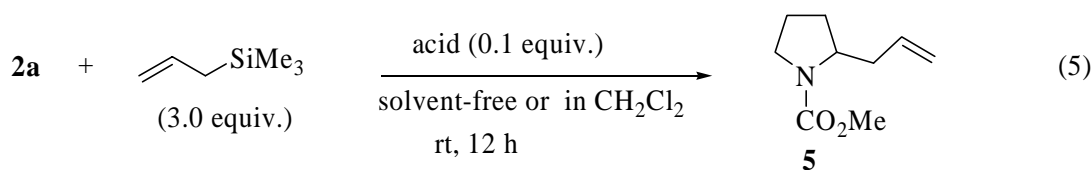
Furthermore, we found that the coupling reaction of **2a** with solid 1,3-diketones (**4s-u**) was possible under solvent free conditions (Eq. 3), in which the amount of **2a** was 3 equivalent to 1,3-diketones (**4s-u**) and the yields of the products (**3as-3au**)¹⁴ were obtained based on **4s-u**. The results indicate the advantage of solvent-free conditions in the Mannich-type reaction between **2a** and **4s-u** in comparison with the reaction in CH₂Cl₂ (Eq. 3).

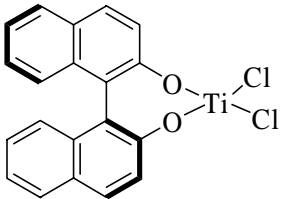


The solvent-free conditions were applicable to the Mannich-type reaction between *N,O*-acetal (**2b**) and (**4p,q,t**) to afford the coupling products (**3bp**, ¹⁴**bq**, ⁸**bt**)¹⁴ in good yields (Eq. 4).



Furthermore, it was found that the yield (57%) of **5** for the solvent-free allylation reaction¹⁵ of **2a** was much superior to that (21%) in CH_2Cl_2 (Eq. 5). In this type of reaction, interestingly, a chiral Lewis acid, (*S*)-BINOL-Ti complex,¹⁶ gave **5** with higher enantioselectivity (enriched isomer; *R*) under solvent-free conditions than that in CH_2Cl_2 , though the ee's were very low.¹⁷



acid	Yield (%) of 5	
	solvent-free	in CH_2Cl_2
<i>p</i> -TsOH	57	21
	75 (20% ee)	66 (11% ee)
	enriched isomer : <i>R</i>	

Although there have not been any data to explain the reason why solvent-free conditions gave higher yields of products than those in CH_2Cl_2 in the Mannich-type reaction between *N,O*-acetals (**2a,b**) and carbon nucleophiles (**4p-u**), we presume that it might be due to faster trapping of *N*-acyliminium ions generated from **2a,b** with **4p-u** than in the reactions in CH_2Cl_2 because of high density of nucleophiles under solvent-free conditions.

In summary the Mannich-type reactions for *N,O*-acetals (**2a,b**) under solvent-free conditions proceeded more efficiently than in CH_2Cl_2 . The characteristics and advantages of the Mannich-type reaction under solvent-free conditions will be applied into preparations of some biologically important α -substituted cyclic amine derivatives.

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 10. A typical experimental procedure under solvent-free conditions: Under an aerobic atmosphere, to a mixture of *N,O*-acetal (**2a**) (1 mmol, 159 mg) and acetylacetone (**4p**) (3 mmol, 300 mg) was added TiCl₄ (0.1 mmol, 0.197 mL) at room temperature. After stirring for 12 h, the reaction mixture was subjected on chromatography (silica gel, ethyl acetate:*n*-hexane=1:3) to afford **3ap** in 89% yield.
 11. **3ap** under solvent-free conditions in the presence of MeOH (1 equiv.) and TiCl₄ (0.1 equiv.) or in CH₂Cl₂ containing MeOH (1 equiv.) and TiCl₄ (0.1 equiv.) was stable.
 12. A little bit lower yields of **3aq** and **3ar** under solvent-free conditions than in CH₂Cl₂ (entries 6 and 9) is hardly rationalized.
 13. The dependency of the yields of **3ap-3r** on nucleophiles (**4p-r**) (entries 4, 8 and 11) can be explained in terms of the high degree of enolization of 1,3-diketones and β-keto esters in comparison with malonic acid esters: A. Gero, *J. Org. Chem.*, 1954, **19**, 1960.
 14. ¹H NMR (CDCl₃, δ) spectral data of new compounds are shown below.
3as: 1.60-2.33 (m, 4H), 2.19 (s, 3H), 2.85-3.80 (m, 2H), 3.66 and 3.69 (2s, 3H), 4.30-4.40, 5.10-5.18 and 5.58-5.62 (3m, 1H), 4.65-4.80 (m, 1H), 7.38-7.65 (m, 3H), 7.82-8.11 (m, 2H).
3at: 1.62-1.82 (m, 2H), 2.00-2.28 (m, 1H), 2.35-2.48 (m, 1H), 2.85-3.10 (m, 1H), 3.25-3.50 (m, 1H), 3.58 and 3.61 (2s, 3H), 4.58-4.82 (m, 1H), 5.78 and 6.40 (2d, *J*=4.0 and 4.0 Hz, 0.25H and 0.75H), 7.38-7.62 (m, 6H), 7.85-8.05 (m, 4H).
3au: 1.49-2.63 (m, 10H), 3.40-3.80 (m, 5.5H), 4.69-4.78 (m, 1H), 10.78 (br s, 0.5H).
3bp: 1.78-2.30 (m, 4H), 2.17 (br s, 6H), 3.30-3.40 (m, 1H), 3.45-3.52 (m, 1H), 4.00-4.50 (m, 1H), 4.45 (br s, 1H), 5.13 (br s, 2H), 7.36 (s, 5H).
3bt: 1.62-2.50 (m, 4H), 2.90-3.00 (m, 1H), 3.10-3.55 (m, 1H), 4.60-4.75 (m, 1H), 4.98-5.30 (m, 2H), 7.20-7.45 (m, 10H), 7.50-7.58 (m, 2H), 7.65-7.75 (m, 1H), 7.90-8.00 (m, 2H).
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17. The ee's were determined by a chiral HPLC method: Daicel Chiralcel OJ (4.6 mm ϕ , 25 cm), *n*-hexane, flow rate: 1.0 mL/min, detection at 210 nm, retention time: 10 min for (*R*)-(+)-isomer and 13 min for (*S*)-(-)-isomer.