

# 29<sup>th</sup> Symposium on Chemistry Postgraduate Research in Hong Kong

## Methylation with Dimethyl Carbonate/Dimethyl Sulfide Mixtures: An Integrated Process without Addition of Acid/Base and Formation of Residual Salts

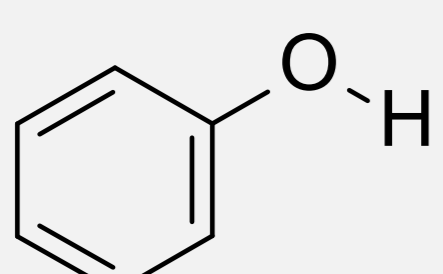
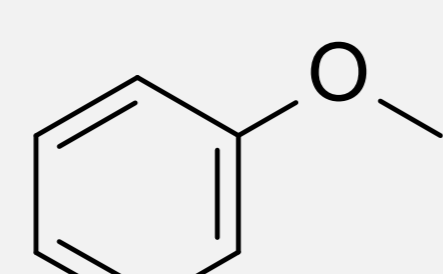
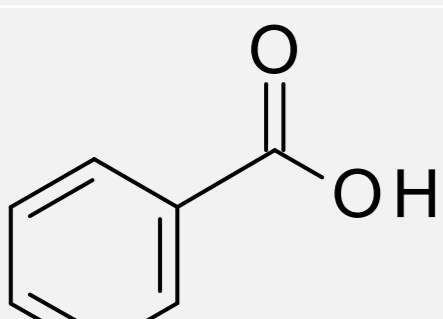
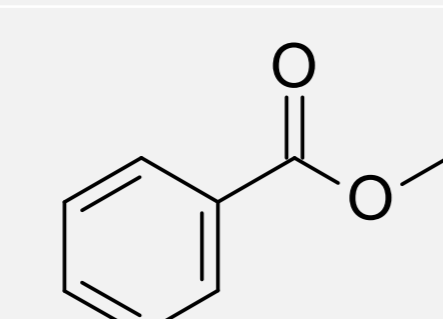
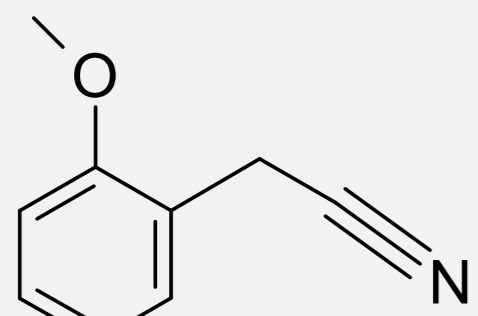
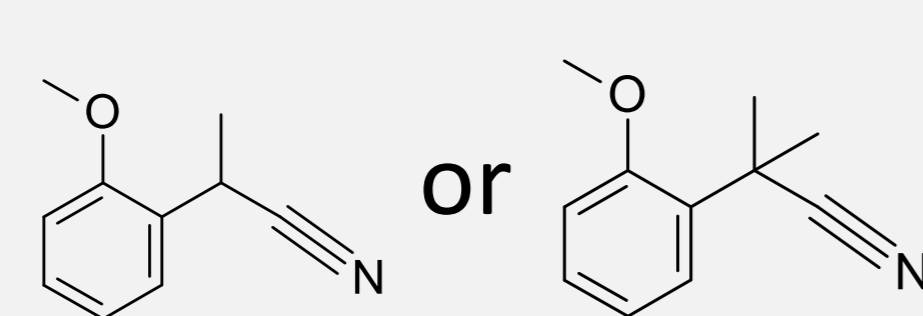
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### INTRODUCTION

- ❖ *O*-methylation produces valuable intermediates for the production of fine chemicals. *C*-methylation of arylacetonitriles helps provide intermediates in drug molecules production.
- ❖ Traditional methylation always involve the use toxic methyl halides and dimethyl sulfate, also leading to the production of waste salts.
- ❖ Dimethyl carbonate (DMC) is regarded as a green methylating agent and solvent that can be synthesized by oxidative carbonylation of methanol (MeOH), which is formed after methylation with DMC.
- ❖ Brønsted base catalysts are employed in methylation with DMC. Although greener methylating agent is used, waste salts are still generated with  $[\text{OCO}_2\text{Me}]^-$  or  $[\text{OMe}]^-$  anions.
- ❖ Dimethyl sulfide ( $\text{Me}_2\text{S}$ ) has low toxicity, is abundant, biodegradable and inexpensive. It can be synthesized from bio-renewable source and also dehydration of MeOH with hydrogen sulfide.
- ❖ This study:  $\text{Me}_2\text{S}$  as a non-basic organocatalyst, DMC as the methylating agent and solvent

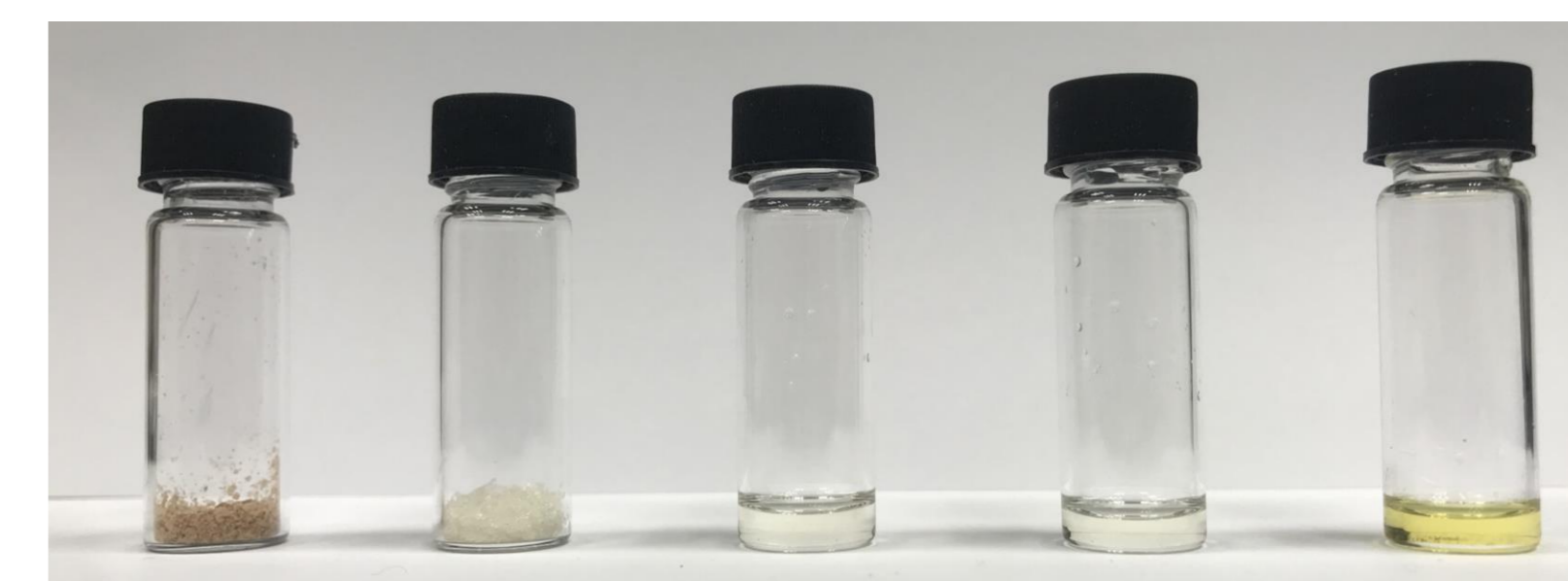
### CONVERSION

- ❖ Most *O*-methylation of phenols and benzoic acids and *C*-methylation of arylacetonitriles were conducted at 220°C for 4 hours
- ❖ Selective yields were shown as follows:

Substrate	Product	NMR yield [%]
		quant. (99)
		99 (99)
		99 (99) or <1

### PURIFICATION

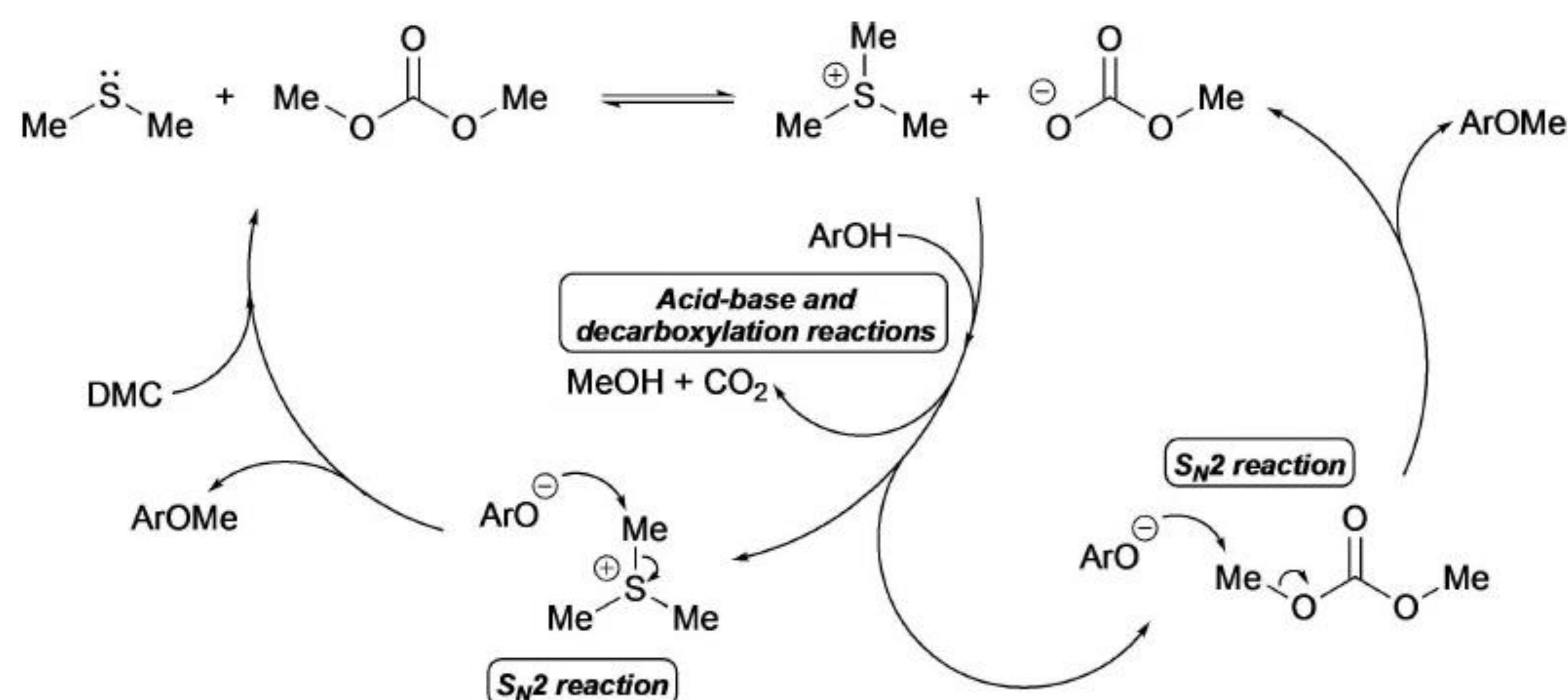
- ❖ Straight forward method: distilling volatile components in the crude product mixtures, e.g.  $\text{Me}_2\text{S}$ , MeOH and DMC. Clean solids/liquids were obtained:



- ❖ Advantages:
  - Conversions were highly selective
  - No acids/bases were used
  - Absence of residual salts
  - $\text{Me}_2\text{S}$  could be recycled easily by distillation
- minimizes generation of wastes

### MECHANISM

- I. Nucleophilic reaction between methylating agents DMC and  $\text{Me}_2\text{S}$  to form  $[\text{Me}_3\text{S}]^+$  and  $[\text{OCO}_2\text{Me}]^-$  ions
- II.  $[\text{OCO}_2\text{Me}]^-$  ions undergo acid-base and decarboxylation reactions with the substrates to break down into MeOH and  $\text{CO}_2$  and phenoxides formed
- III. Depends on the initial  $\text{Me}_2\text{S}/\text{DMC}$  ratio, methylation would proceed through  $\text{S}_{\text{N}}2$  reaction by DMC or  $[\text{Me}_3\text{S}]^+$



### CONCLUSION

- ❖ Bio-renewable, inexpensive catalyst/co-reagent  $\text{Me}_2\text{S}$  was used for the methylation of phenols, benzoic acids and arylacetonitriles
- ❖ DMC acted as a solvent/reagent
- ❖ No extra Brønsted base was needed
- ❖ Active intermediate  $[\text{Me}_3\text{S}]^+ [\text{OCO}_2\text{Me}]^-$  was formed
- ❖  $\text{Me}_2\text{S}$  was regenerated after reacting with the substrates
- ❖ Final product could be isolated in good purity by simple distillation

### Reference

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