Efficient synthesis of Heterophanes by intramolecular cycloaddition of bis(acylketene)s

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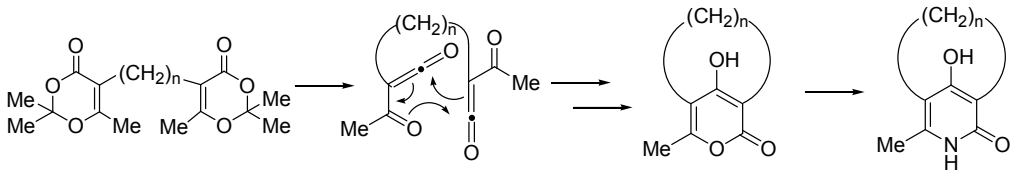
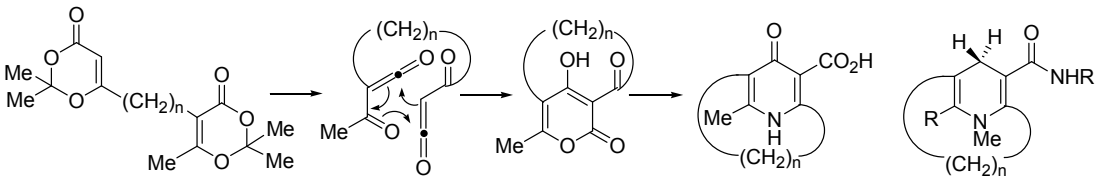
I developed a new synthetic method of bridged pyridine derivatives. The key step of this method is intramolecular [4+2] cycloaddition of bis(acylketene) derivatives **2a**,**b** thermally generated from 1,3-dixoxin-4-ones **1a**,**b** to give bridged pyrones. Thus, **1a**,**b** were heated in refluxing bromobenzene under a high-dilution condition, and the product mixtures were heated with water to afford pyrone **3a**,**b**. On heating with ethanolic ammonia, **3a,b** were transformed into pyridone **4a**,**b** in high yields.



1a (n = 10)
1b (n = 12)

2a,**b** **3a**,**b** **4a**,**b**

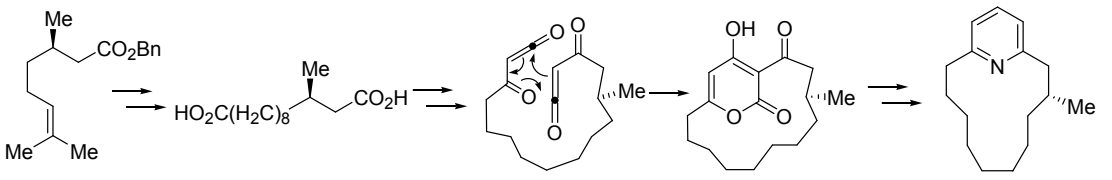
Unsymmetrical bis(acylketene)s **6a**,**b** generated from the corresponding 1,3-dioxin-4-ones **5a,b** also underwent intramolecular [4+2] cycloaddition to give bridged pyrones **7a**,**b**. The ring transformation of **7a**,**b** by heating with ethanolic ammonia afforded *para*-pyridinophanes **8a**,**b** which are expected to serve as new intermediates for planar chiral NADH models.



5a (n = 10)
5b (n = 11)

6a,**b** **7a**,**b** **8a**,**b** NADH model

The *meta*-pyridinophane derivative (*R*)-(+)-muscopyridine **13** is one of the odoriferous constituents of natural musk obtained from the male musk deer *Moschus moschiferus.* The synthesis of **13** has been accomplished using the ketene cycloaddition in 12 steps with 47% overall yield.



9 **10** **11** **12**

(*R*)-(+)-muscopyridine 13
(47%: 12 steps)