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An easy and efficient method for the synthesis of 2,2-dialkyl-3-nitrochromene

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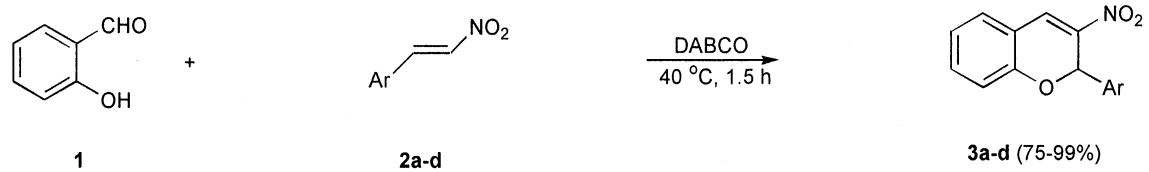
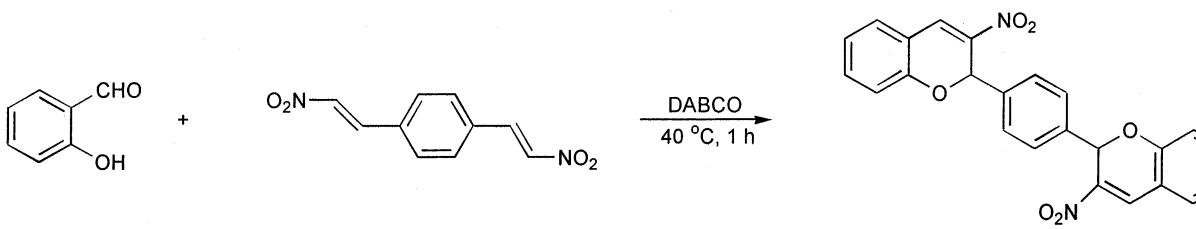
Abstract—Reactions of salicylaldehyde **1**, 1,4-diazabicyclo[2.2.2]octane (DABCO), with β-nitrostyrenes **2**, **4**, **12**, **14**, and **16**, respectively, in the absence of solvent at 40°C gave high yields of 3-nitro-chromenes. Only 96% of *trans*-3-nitro-4-hydroxyflavans **7** or 98% of **10** were isolated when compounds **6** or **9** reacted with **1** and DABCO under similar conditions. When the reaction temperature was increased to 90°C, **7** and **10** underwent dehydration to generate 74% of **8** and 89% of **11**.

The synthesis[1] and biological activity[2] of 3-nitrochromenes have been reported because of their potential as precursors to a variety of medically important 2*H*-benzopyran derivatives such as flavonols,[3] amines,[4] etc. It also has been reported that Δ^3-chromenes containing electron-withdrawing substituents at the 3-position possess radio-protecting properties[5] and 3-nitrochromenes with appropriate substituents are potential candidates for nonlinear optical applications.[6] However, 2,2-dialkyl-3-nitrochromenes are not well studied yet. Herein, we provide an improved, easy, and efficient method to prepare 2,2-dialkyl-3-nitrochromenes. It is useful not only in the past works of synthesizing 3-nitro-2-phenyl-2*H*-chromenes, but also in our current studies of the synthesis of 2,2-dialkyl-3-nitrochromenes.

Our recent study found that high yields of 3-nitrochromenes **3a–d** (**a**: Ar = Ph, 98%; **b**: Ar = *p*-$MeOC_6H_4$, 75%; **c**: Ar = *p*-ClC_6H_4, 99%; **d**: Ar = thiophene, 79%) could be generated from the reaction mixture of salicylaldehyde **1** (4–10 equiv.), β-nitrostyrenes **2a–d** (1 equiv.; **a**: Ar = Ph, **b**: Ar = *p*-$MeOC_6H_4$, **c**: Ar = *p*-ClC_6H_4, **d**: Ar = thiophene) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (0.5–1.0 equiv.) in the absence of solvent at 40°C for 1.5 h (Eq. (1)).



1 **2a-d** **3a-d** (75-99%) (1)



1 **4** **5** (99%) (2)

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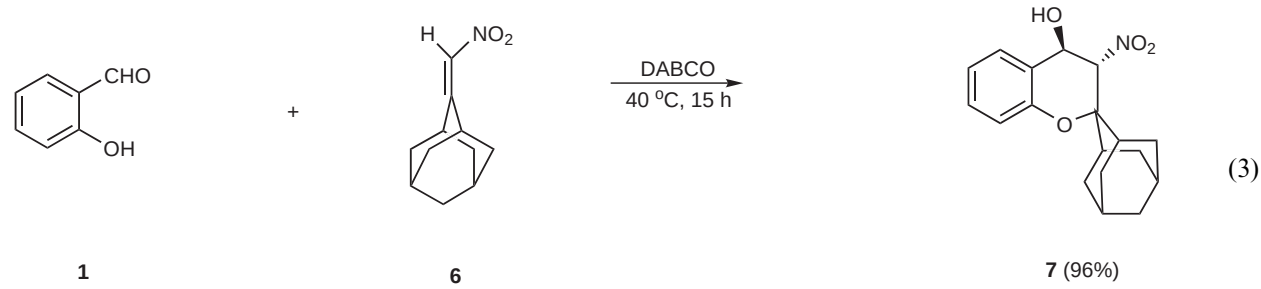
Under similar conditions, 99% of **5** also could be isolated when compound **4** was used (Eq. (2)). The structures of **3** and **5** could be assigned according to their ^{1}H and ^{13}C NMR.

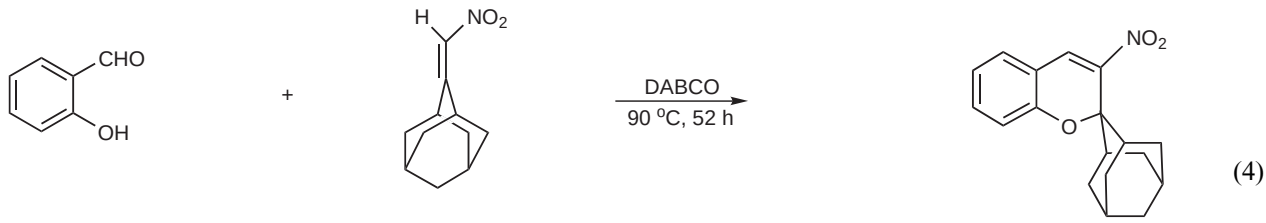
On the basis of Eqs. (1) and (2), we then focussed our studies on the reactions of **1** with more steric hindrance substrates, 2,2-disubstituted-1-nitroalkenes, which were little studied in the literatures and only the derivatives of 2,2-dimethyl-3-nitrochromenes were mentioned in these papers.[7] When **1** reacted with compounds **6** and **9**,[8] respectively, in the presence of DABCO under similar conditions, to our surprise, the isolated products were not 3-nitrochromenes **8** and **11**, but only high yields of 3-nitro-4-hydroxyflavans **7** (96%) and **10** (98%) were separated (Eqs. (3) and (5)). The *trans* structures of the nitro alcohols **7** and **10** were also determined by their ^{1}H NMR spectrum; $J_{3,4}=6.0$ Hz for both **7** and **10**.[1b] The generation of the different products **3** and **5** or **7** and **10** probably can be explained by the steric effect of the groups in the 2-position of flavan and this effect plays an important role in both the reaction conditions and the stability of products. To overcome the steric effect, the temperature was increased to 90°C, and the expected 3-nitrochromenes (74% of **8** and 89% of **11**) were produced from further dehydration of **7** or **10** (Eqs. (4) and (6)). According to the above results, we can conclude that this method is easy for us to obtain either 3-nitro-4-hydroxyflavans or 3-nitrochromenes just by controlling the reaction temperature when steric substrates **6** and **9** are used. When DABCO was replaced by triethylamine (1 equiv.) in Eqs. (3) and (4), similar results were also observed and the yield of **7** was 99% at 40°C for 20 h and the yields of **7** and **8** were 20% and 75% at 90°C for 77 h. This result indicates that DABCO is superior to triethylamine under similar conditions.

When **1** reacted with 2,2-disubstituted-1-nitroalkenes, **12**, **14**,[8] and **16**,[9] respectively, in the presence of



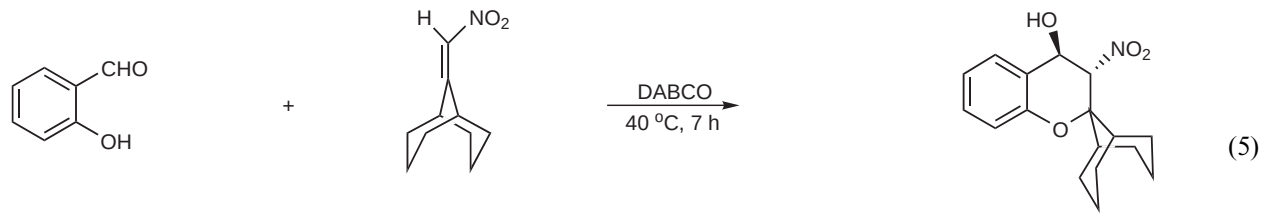
(3)

1 **6** **7** (96%)



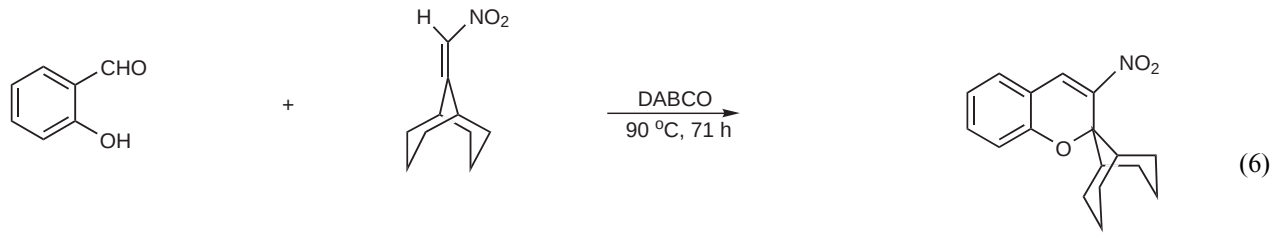
(4)

1 **6** **8** (74%)



(5)

1 **9** **10** (98%)



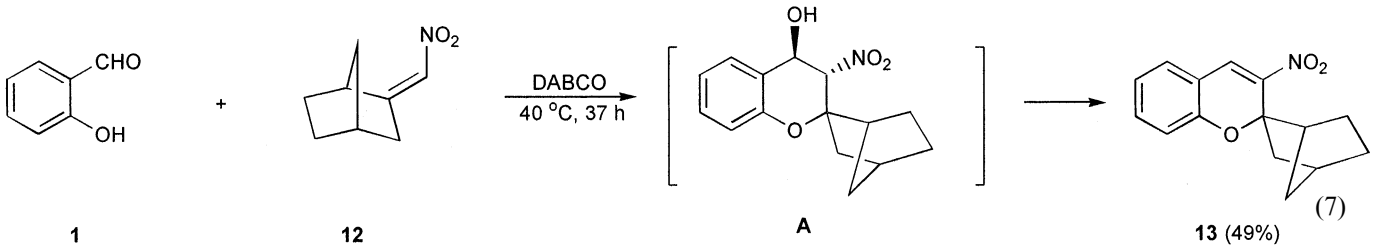
(6)

1 **9** **11** (89%)

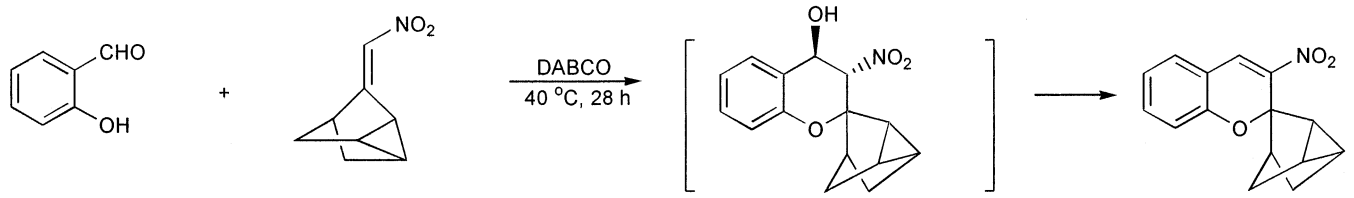
DABCO under similar conditions, 49–99% of 2,2-dialkyl-3-nitrochromenes, such as **13**, **15**, or **17**, were obtained (Eqs. (7)–(9)). It is believed that all the reactions (Eqs. (7)–(9)) also proceed through the dehydration of the intermediates **A**–**C** to obtain 3-nitrochromenes only at 40°C as described above.

Although this method is useful in the preparation of some 2,2-dialkyl-3-nitrochromenes, not all 2,2-disubstituted-1-nitroalkenes generate the same results as Eqs. (3)–(9). For example, when **18**–**20**, and **34**–**36**[9] were used, the results were complicated and the products were **21**–**33** (Eqs. (10)–(11)).

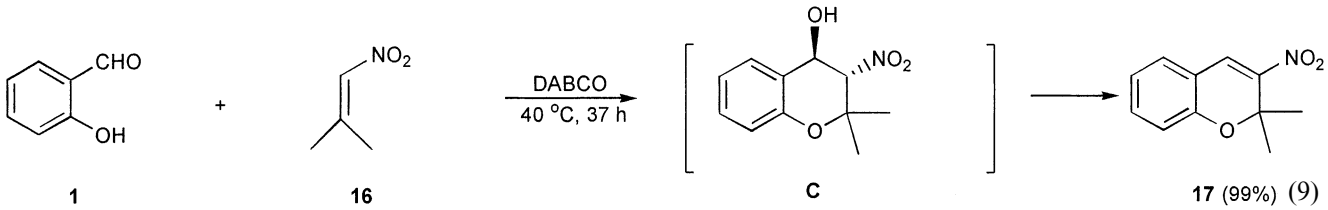
To prove the equilibrium between allyl nitro compounds **34**–**36** and nitroalkenes **18**–**20**, 1-nitropropene **37** and 3-nitroprop-1-ene **39** were used to react with **1** under similar conditions and only the same product **38** was produced at room temperature (Eqs. (12) and (14)). At 40°C, only 30% of **38** was obtained from the reac-



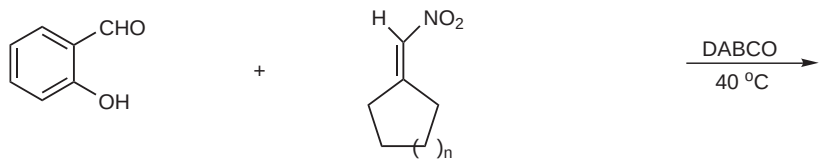
1 **12** **A** **13** (49%) (7)



1 **14** **B** **15** (99%) (8)

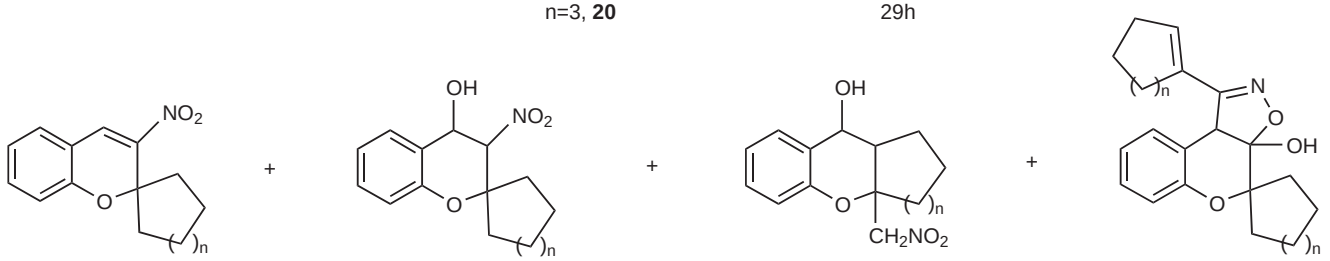


1 **16** **C** **17** (99%) (9)



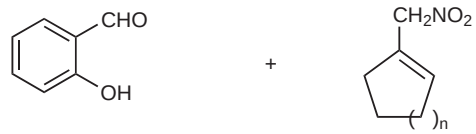
1

n=1, **18** — 3h
n=2, **19** — 36h
n=3, **20** — 29h

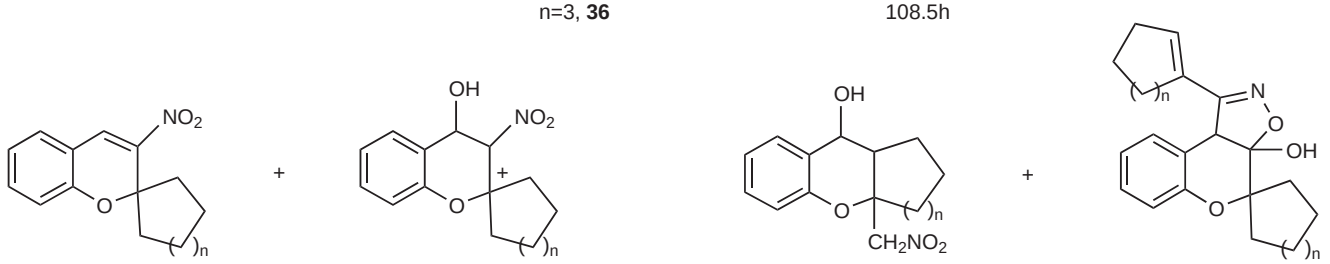


n=1, **21** (12%)	**24** (24%)	two isomers observed **26** (28%), **27** (23%)	**31** (4%)
n=2, **22** (14%)	**25** (8%)	-	**32** (22%)
n=3, **23** (trace)	-	three isomers observed **28** (20%), **29** (20%), **30** (18%)	**33** (12%)

(10)



1 n=1, **34**; n=2, **35**; n=3, **36** — 1.5h; 7.5h; 108.5h



n=1, **21** (6%)	**24** (14%)	**26** (31%), **27** (27%)	**31** (3%)
n=2, **22** (8%)	**25** (trace)	-	**32** (14%)
n=3, **23** (trace)	-	**28** (26%), **29** (22%), **30** (11%)	**33** (8%)

(11)

1 + **37** → **38** (56%) (12)

1 + **37** → **38** (30%) (13)

1 + **39** → **38** (24%) (14)

tion of **1** and **37** for 20 min (Eq. (13)). The difference between Eqs. (12) and (13) indicates that lowering the reaction temperature can increase the yield of **38**.

In conclusion, this method is easy and useful not only in the synthesis of 3-nitro-2-phenyl-2*H*-chromenes but also in the preparation of 2,2-dialkyl-3-nitrochromenes. Our current work is focusing on the reaction mechanism and the stereoselectivity and will be reported in the future.

Acknowledgements

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