A mild and facile synthesis of cyclic imides using pyridinium chlorochromate

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A mild and facile synthetic method of cyclic imides is presented. These compounds are widely used in the synthesis of novel medical, polymeric, photonic and electronic materials. Compared with traditional syntheses, the method reported has several advantages including mild conditions, simplified work-up and low cost.

Keywords: cyclic imides, pyridinium chlorochromate, synthesis

Cyclic imides and their derivatives are widely used in the synthesis of novel medical,[1] polymeric,[2] photonic,[3] and electronic materials.[4] However, the mild, simple and general routes for the synthesis of cyclic imides and their derivatives are limited.[5] Typical methods are the dehydrative condensation of an anhydride with an amine at high temperature[6] and the cyclisation of the amic acid in the presence of acidic reagents.[7] Recently, there have been reports of the synthesis of 2-benzamido-*N*-methyl-2-vinylsuccinimide by oxidiation of a hydroxy amide with pyridinium dichromate (PDC) in DMF,[8] the ring expansion of 4-formyl-β-lactams for the synthesis of succinimide derivatives,[9] the ruthenium- or palladium-catalysed carbonylation of aromatic compounds leading to phthalimides,[10] ruthenium-hydride-based catalysed reaction simple diols with amine,[11] 2,2,6,6-tetramethylpiperidine 1-oxyl and iodobenzene diacetate catalysed oxidative cyclisation of hydroxy amide.[12] Nevertheless, each of these routes has synthetic problems such as complex work-ups, the limited availability of suitably functionalised starting materials, difficulty in catalyst preparation and high cost.

Pyridinium chlorochromate (PCC) is a versatile oxidising agent, which has often been employed in the selective oxidation of various alcohols.[13] It has also been utilised in the transposition of tertiary alcohols and cyclopropyl methanols.[14] During our investigation into the total synthesis of (+)-grandisol,[15] the sex pheromone of the cotton boll weevil, we needed 5-oxopentanamide **3b**. Interestingly, when we attempted to oxidise 5-hydroxypentanamide **1b** to its corresponding aldehyde **3b** with PCC, glutarimide **2b** was obtained as the unexpected product; the desired aldehyde **3b** was not detected (Scheme 1). Compared with the methods described above, this synthetic method using PCC has several advantages including mild conditions, simplified work-ups and low cost. We now report a mild and facile synthesis of cyclic imides using PCC.

Results and discussions

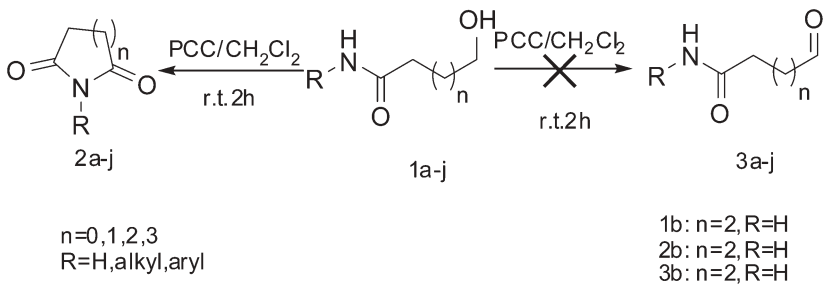
The hydroxy amide **1b** was prepared by treatment of δ-valerolactone with ammonia in MeOH at room temperature. The oxidation of hydroxyl-terminated amide **1b** was then achieved with 3 equiv. of PCC and silica gel in CH_2Cl_2 with stirring at room temperature for 24 h to give glutarimide **2b** in moderate (70%) yield. Due to the limited solubility of PCC in CH_2Cl_2, the PCC oxidation is a heterogeneous process. In 1989, Adams *et al.*[16] reported the use of ultrasound technology in PCC oxidation resulted in an increased yield and rate of oxidation. Thus, ultrasound was applied to our reaction conditions. Using the same molar ratio as above, an oxidation experiment was carried out with ultrasonic irradiation at room temperature. Within 2 h, the isolated yield of glutarimide **2b** was improved to 80%.

We also examined the reactions of hydroxy amides (**1a**, **1c**, **1d**) with PCC under ultrasonic irradiation. Table 1, shows that 4-hydroxybutanamide **1a** reacted with PCC to produce succinimide **2a** in good yield. Adipimide **2c** was achieved with a low yield from 6-hydroxyhexanamide **1c** whereas the four-membered ring compound **2d** was not obtained. Reactions of this type generally lead to easier formation of the five-membered ring than of the six-membered ring and formation of the six-membered ring is favoured over the seven-membered ring. Under the oxidative conditions described above, it was also observed that various *N*-substituted hydroxy amides **1e–2j** were reacted with PCC. As shown in Table 1,

Table 1 Reactions of hydroxy amides with PCC under ultrasonic irradiation

Entry	Hydroxyl amides	Product	Yield[a] /%
1	**1a** R=H, *n*=1	**2a**	85
2	**1b** R=H, *n*=2	**2b**	80
3	**1c** R=H, *n*=3	**2c**	29
4	**1d** R=H, *n*=0	**2d**	ND
5	**1e** R=CH_3, *n*=1	**2e**	81
6	**1f** R=CH_2CH_3, *n*=1	**2f**	74
7	**1g** R=$CH_2CH_2CH_3$, *n*=1	**2g**	72
8	**1h** R=$CH(CH_3)_2$, *n*=1	**2h**	69
9	**1i** R=CH_2Ph, *n*=1	**2i**	70
10	**1j** R=$C(CH_3)_3$, *n*=1	**2j**	ND

ND, Not detected.
[a]Isolated yield.



Scheme 1 Reaction of hydroxy amides with PCC.

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these oxidation reactions afforded *N*-substituted cyclic imides **2e–i** in good yields. The very sterically hindered *N-tert*-butyl-4-hydroxybutanamide **1j** gave no detectable cyclic imides. Various cyclic imides were obtained in moderate to good yields (69–85%) using the method, which were similar or a bit better than the yields (14–88%) obtained by traditional methods.[6–12]

In conclusion, we have reported a mild and facile method for synthesis of cyclic imides by oxidative cyclisation of hydroxy amides with PCC under ultrasonic irradiation. In addition, a wide variety of cyclic imides were obtained in moderate to good yields with the method. The synthetic method has several advantages compared to the previous methods including mild conditions, simplified work-ups and low cost.

Experimental

Reagents and solvents were obtained from commercial suppliers. All reactions were carried out under air and monitored by TLC using commercial aluminum-backed silica gel plates. The ultrasonic reactions were performed in ultrasonic cleaner (KQ5200DE, 70W) with frequency of 40 MHz. Melting points were observed on YRT-3 Melting Point Tester and are uncorrected. NMR spectra were recorded on Varian Inova-400/500 MHz NMR spectrometer with TMS as an internal reference. MS were recorded on a LCQ Advanted MAX mass spectrometer. Silica gel (200–300 mesh) was used for the oxidation reactions and column chromatography.

General procedure

Hydroxyl amides (**1a–j**) were obtained by the reactions of lactones with ammonia or amine in MeOH at room temperature.[17] The preparation of cyclic imides (**2a–j**): A magnetically stirred hydroxyl-terminated amides (20 mmol) was added to a homogeneous mixture of PCC (60 mmol) and silica gel (same weight as PCC) in CH_2Cl_2 (200 mL), and the reaction was stirred for 2 h at room temperature with ultrasonic irradiation. The reaction mixture was then filtered through a pad of silica gel column using CH_2Cl_2 as the eluent. The solvent was evaporated and the residue was purified on a silica gel column using PE–EtOAc (1:3) as the eluent furnished cyclic imides.

Succinimide (**2a**): White solid, m.p. 124–127 °C (lit.[18] 125–127 °C). ^{1}H NMR (500 MHz, CD_3Cl): δ = 2.76 (4H, s, $2COCH_2$), 8.88 (1H, s, NHCO). ^{13}C NMR (125 MHz, CD_3Cl): δ = 178.15 (2C=O) and 29.82.

Glutarmide (**2b**): White solid, m.p. 149–151 °C (lit.[18] 154–157 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.98–2.04 (m, 2H), 2.58–2.61 (m, 4H, $2COCH_2$), 8.30 (s, 1H, NHCO). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.94 (2C=O), 31.86 and 18.09. MS (*m/z*, %): 114.1 (M^++1).

Adipimide (**2c**): White solid, m.p. 161–163 °C (lit.[18] 167–172 °C). ^{1}H NMR (500 MHz, CD_3OD): δ = 1.91 (4H, s), 2.75 (4H, s, $2COCH_2$). ^{13}C NMR (125 MHz, CD_3OD): δ = 176.30 (2C=O), 34.22 and 20.13.

N-methylsuccinimide (**2e**): White solid, m.p. 67–68 °C (lit.[19] 70–71 °C). ^{1}H NMR (400 MHz, CD_3Cl): δ = 2.68 (4H, s, $2COCH_2$), 2.95 (3H, s, NCH_3). ^{13}C NMR (100 MHz, CD_3OD): δ = 177.21 (2C=O), 28.16 and 24.69.

N-ethylsuccinimide (**2f**): Colourless oil, ^{1}H NMR (400 MHz, CD_3OD): δ = 0.93–0.97 (3H, m), 2.53 (4H, s, $2COCH_2$), 3.31–3.36 (2H, m, NCH_2); ^{13}C NMR (100 MHz, CD_3OD): δ = 177.04 (2C=O), 33.42, 28.04 and 12.74.

N-propylsuccinimide (**2g**): Colourless oil, ^{1}H NMR (400 MHz, CD_3Cl): δ = 0.60–0.63 (3H, m), 1.25–1.34 (2H, m), 2.44 (4H, s, $2COCH_2$), 3.14–3.17 (2H, m, NCH_2). ^{13}C NMR (100 MHz, CD_3Cl): δ = 177.18 (2C=O), 39.94, 27.89, 20.70 and 10.94.

N-isopropylsuccinimide (**2h**): White solid, m.p. 95–96 °C (lit.[20] 95–97 °C). ^{1}H NMR (400 MHz, CD_3Cl): δ = 1.36 and 1.37 (6H, 2s), 2.63 (4H, s, $2COCH_2$), 4.33–4.40 (1H, m, NCH). ^{13}C NMR (100 MHz, CD_3Cl): δ = 177.17 (2C=O), 43.69, 28.05 and 19.11.

N-benzylsuccinimide (**2i**): White solid, m.p. 102–103 °C (lit.[21] 104–105 °C). ^{1}H NMR (400 MHz, CD_3Cl): δ = 2.63 (4H, s, $2COCH_2$), 4.61 (2H, s, NCH_2), 7.24–7.37 (5H, m, 5 CH of benzene). ^{13}C NMR (100 MHz, CD_3Cl): δ = 176.84 (2C=O), 135.90, 128.78, 128.57, 127.86 (6 C benzene), 42.30 and 28.18.

Received 1 October 2011; accepted 25 October 2011
Paper 1100914 doi: 10.3184/174751911X13202290249578
Published online: 22 November 2011

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