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# Annulation of heterocyclic secondary enamines with dicarboxylic acid dichlorides, an unexpected ring size effect

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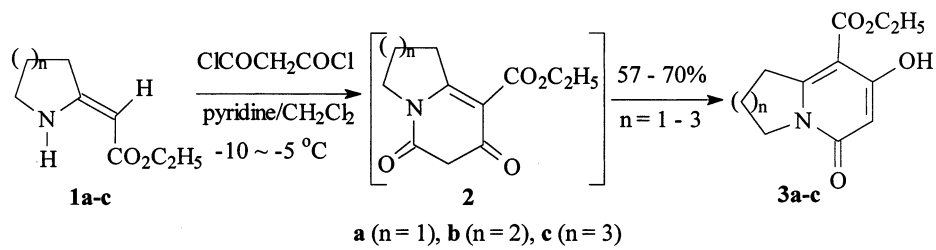
**Abstract**—Under very mild conditions heterocyclic secondary enamines react efficiently with malonyl chloride to produce hydroxylated 2-pyridinone-fused heterocycles. The reactions of enamines with oxalyl chloride, however, afford varied products depending upon the heterocyclic structure of the enamine. Whilst a *C*-acylated enamine and a lactam-fused heterocycle were obtained from the reaction of the five- and seven-membered heterocyclic enamines, respectively, the six-membered heterocyclic enamine gave 2-oxo-5,6,7,8-tetrahydro-2*H*-pyrido[3,2-*b*]pyran. The reaction mechanisms are discussed. © 2001 Elsevier Science Ltd. All rights reserved.

Heterocyclic secondary enamines **1**, also known as exocyclic enaminoesters, are useful building blocks for the synthesis of natural products. In the 1960s, Eschenmoser and co-workers[1] pioneered the chemistry of heterocyclic enamines during their synthetic studies of corrins. They used the reaction of an enaminonitrile with an iminoether as one of the key steps in the construction of the corrin ring system. Since the late 1970s, heterocyclic enamines have been investigated by Kishi,[2] Danishefsky,[3] Rapoport[4] and others in the synthesis of saxitoxin, camptothecin, mitomycins and alkaloids.[5–8] Recently, a synthesis of carbacephems, a new class of β-lactam antibiotics, has been reported[9] by reducing the double bond of exocyclic enaminoesters followed by intramolecular cyclization.

One of the most noticeable features of heterocyclic secondary enamines **1** is their bisnucleophilicity; when treated with biselectrophilic reagents, enamines **1** undergo annulation reactions via the enaminic carbon and the secondary amino nitrogen to give fused heterocyclic compounds. Much attention has been given therefore to the reaction of enamines **1** with α,β-unsaturated compounds[3,4,7,10–12] and a systematic study of such annulation reactions has appeared very recently.[13] Surprisingly, no reaction of heterocyclic secondary enamines with dicarboxylic acid dichlorides, simple and strong biselectrophilic species, has been reported yet. We envisaged that, however, annulation of enamines **1** through diacylation using dicarboxylic acid dichlorides would produce polyfunctionalized fused heterocyclic derivatives that are valuable precursors to hydroxylated pyrrolizidine[14] and indolizidine[15] alkaloids such as rosmarinecine and castanospermine and their analogues.

The only example[16] of the reaction of a heterocyclic secondary enamine with a dicarboxylic acid derivative




**Scheme 1.**

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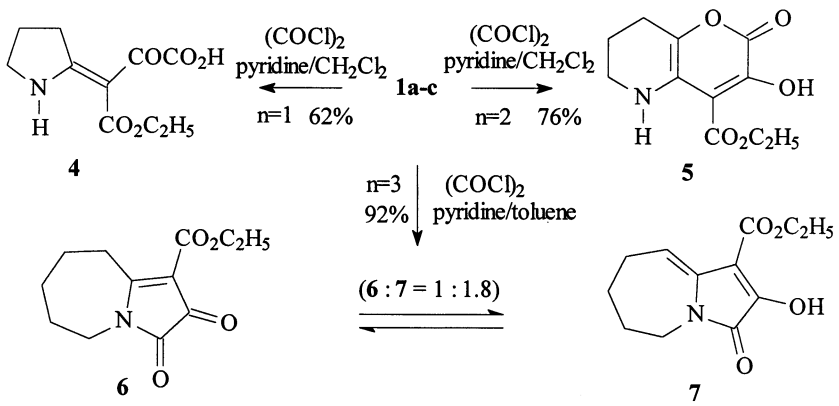
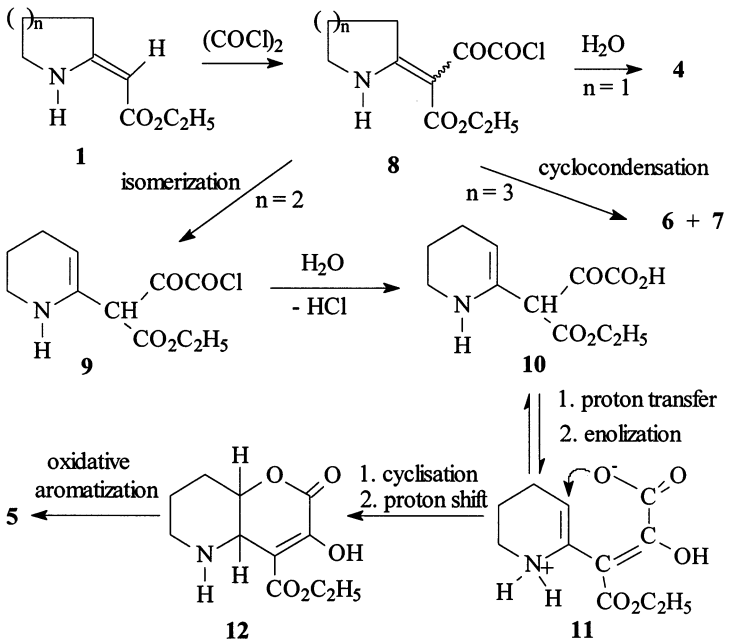



**Scheme 2.**

is the annulation reaction at high temperature (155°C) between 2-pyrrolidylidene acetate **1a** ($n=1$) and substituted di-2,4,6-trichlorophenyl malonates. To start our study, we first chose the cheap and commercially available malonyl chloride as the biselectrophilic reagent. We found that the heterocyclic secondary enamines **1a–c** underwent smooth reactions with malonyl chloride at below −5°C. In the presence of pyridine as an acid scavenger, the annulation reactions proceeded rapidly and effectively to afford hydroxylated 2-pyridinone fused heterocycles **3** as the sole products in good yields (Scheme 1).

In contrast to the reactions observed for malonyl chloride, we encountered totally different chemistry when oxalyl chloride was utilized as the diacylation reagent under identical conditions. The reaction between enamine **1** and oxalyl chloride was strongly dependent upon the structure of the enamines. Whilst the five-membered heterocyclic enamine **1a** gave the *C*-acylated product **4**, the seven-membered reactant **1c** yielded a condensed heterocyclic product. As evidenced by the spectroscopic data,[17] the resulting fused heterocycle existed as an equilibrium mixture of the pyrrole-2,3-dione **6** and the pyrrol-2-one **7**, with the latter being the dominant isomer. Interestingly, in the case of the six-membered heterocyclic enamine **1b**, the unexpected pyranone **5**[18] was isolated as the sole product (Scheme 2). It should also be noted that in all cases no *N*-acylated products were obtained regardless of the ring size of the heterocyclic enamines **1**. This is different from the acylation reactions of enamines **1** using mono-carboxylic acid halides, which have been reported to give rise to *C*- and/or *N*-acylated products depending on the heterocyclic structure of the enamine.[19]

Compound **4** apparently results from hydrolysis of the initially formed *C*-acylated intermediate **8** ($n=1$), while the formation of products **6** and **7** was most probably effected by the cyclization of the intermediate **8** ($n=3$). The energy gained from both aromatization and intramolecular hydrogen bond formation[17] between the hydroxy and carbonyl groups stabilizes the hydroxylated pyrrol-2-one structure, giving **7** as the major




**Scheme 3.**

isomer in equilibrium. To account for the formation of the pyranone product from the six-membered enamine **1b**, a reaction mechanism comprising proton-assisted cyclization and oxidative aromatization is proposed. As depicted in Scheme 3, intermediate **8** ($n=2$) may isomerize to form the tetrahydropyridine **9**. It has been reported[12,19] that six-membered exocyclic enamine derivatives tend to shift their double bond from the *exo*- to the *endo*-position. Being an amino acid, the hydrolysis intermediate **10** would tautomerize into its zwitterionic form **11** that facilitates cyclization of the carboxylic anion to the enaminium double bond to form lactone **12**. Oxidative aromatization of **12**, caused by atmospheric oxygen, would then lead to the formation of the product **5**. It should be noted that, however, the precise reason for the various reaction pathways for the enamines of the different heterocyclic ring structures remains unclear. This may arise from a combined effect of the nucleophilicity of the secondary amino nitrogen and the tendency of the double bonds of the intermediate **8** to isomerize from the *exo*- to the *endo*-position together with the ring strain generated from the formation of the fused heterocycles. In other words, the ring size of heterocyclic secondary enamines **1** plays an important and subtle part in determining reaction outcome.

In summary, we have provided a general method for the preparation of hydroxylated 2-pyridinone-fused heterocycles from heterocyclic secondary enamines under very mild conditions using malonyl chloride as the biselectrophilic reagent. The reaction of heterocyclic secondary enamines with oxalyl chloride has been shown to give different products depending on the heterocyclic structure of the enamines. Whilst the five- and seven-membered heterocyclic enamines afforded a *C*-acylated enamine and a lactam-fused heterocycle, respectively, 2-oxo-5,6,7,8-tetrahydro-2*H*-pyrido[3,2-*b*]-pyran was produced as the sole product from the six-membered heterocyclic enamine.

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17. Spectroscopic data for **6** and **7**: Mp 83–86°C; (found: C, 60.48; H, 6.38; N, 5.58. $C_{12}H_{15}NO_4$ requires C, 60.75; H, 6.37; N, 5.90). MS (EI) $m/z$ 237 (49%, $M^+$), 163 (61), 191 (100); IR (KBr) 3150, 1720, 1710, 1620 $cm^{-1}$. Two sets of $^1H$ and $^{13}C$ NMR corresponding to **6** and **7** were observed. $^1H$ NMR ($CDCl_3$) $\delta_H$ 9.54 (0.64H, s, br, OH), 6.27 (0.64H, t, $J$ 6.1, C*H*=C), 4.39 (1.28H, q, $J$ 7.1, $OCH_2$), 4.28 (0.72H, q, $J$ 7.1, $OCH_2$), 3.88–3.81 (2H, m, $NCH_2$), 3.39 (0.72H, br, $CH_2C$=C), 2.50 (1.28H, m, $CH_2C$=C), 1.88 (4H, m, $2CH_2$), 1.70 (0.72H, m, $CH_2$), 1.42–1.31 (3H, dt, $J$ 7.1, $CH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta_C$ 185.5, 178.1, 165.9, 162.4, 162.0, 156.5, 133.3, 115.9, 105.6, 103.6, 101.0, 61.6, 60.5, 43.2, 41.3, 30.1, 28.5, 27.7, 27.4, 26.6, 26.4, 25.7, 14.3, 14.3.
18. Spectroscopic data for **5**: Mp 194–195°C; (found: C, 55.26; H, 5.49; N, 5.87. $C_{11}H_{13}NO_5$ requires C, 55.23; H, 5.48; N, 5.85). MS (EI) $m/z$: 239 (17%, $M^+$), 193 (100); IR (KBr) 3550, 3400, 2960, 1650, 1460 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 11.85 (1H, s, OH), 9.64 (1H, s, br, NH), 4.47 (2H, q, $J$ 7.0, $OCH_2$), 3.75 (2H, t, $J$ 5.6, $NCH_2$), 2.54 (2H, t, $J$ 6.2, $CH_2C$=C), 2.05 (2H, m, $CH_2$), 1.44 (3H, t, $J$ 7.0, $CH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 167.3, 158.4, 150.3, 148.6, 110.1, 104.1, 62.8, 38.3, 27.5, 27.1, 14.3.
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