# ACYLATION OF ACYCLIC ENAMINES WITH AN EXCESSIVE AMOUNT OF PYRIDINECARBONYL CHLORIDES

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Abstract----- Acylation of the acyclic enamines (1a and d) and (6a) with an excessive amount of isonicotinoyl or nicotinoyl chloride provided a simple preparation of the spiranes (2, 3, and 7) or the 1,6-naphthyridines (4 and 5) respectively, of which the latter has an analogous structure of nalidixic acid, a powerful antibacterial agent.

Previously [1] we have reported a convenient preparation of synthetically useful spirodihydropyridine derivatives and its application to alkaloid synthesis.

As an extension of our study[1] on acylation of the imine with pyridinecarbonyl chlorides, the present investigation was undertaken to investigate acylation of the aminoacrylates (1a and d) and (6a) as typical examples of acyclic enamines.

Although acylation of ethyl methylaminocrotonate[2] (1a) with an equimolar amount of isonicotinoyl chloride in the presence of triethylamine yielded the C-acylated product (1b), treatment with an excessive amount (ca. 4 moles) of the acid chloride resulted in the formation of a mixture of two types of the spirodihydropyridines (2a and b) and (3) together with a small amount of (1b) which were separated by chromatography on silica gel. Spectral data[3] of the main product (2a) (31 %) and the fact that treatment of (2a) with methanol at room temperature afforded (1b) and methyl isonicotinate proved the structure of the product (2a) which consisted of one part of the enamine (1a) and two parts of the acid moiety. When the C-acylated product (1b) was treated with an excessive amount of isonicotinoyl chloride, the spirane (2a) was also obtained. We therefore suggest that acylation of the enamine (1a) proceeds to give the C-acylated product (1b) predominantly which would then be readily converted into the spirane (2a) under the acylating condition.

Spectral data[4] of the minor product (2b) (3 %) depicted the structure as shown which consisted of one part of the enamine (1a) and three parts of the acid moiety.

Since the second spirane (3) (5 %) was found to be a different type of the spirodihydropyridine from the spectral data[5], it might presumably be formed from N-acylation of the enamine (1a) followed by spontaneous acylation of the pyridine ring of the resulting N-acylated intermediate.

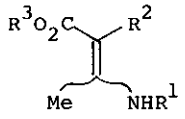
Similar acylation of (1a) with two molar amount of nicotinoyl chloride afforded three types of the products (1c), (4a)[6], and (5)[7] in 10, 40, and 4 % yields respectively. Upon standing in a chloroform solution at room temperature or treatment with 10 % hydrochloric acid, the third product (5) was readily deacylated into the main product (4a). Since attempted cyclization of the C-acylated product (1c) to the corresponding naphthyridones (4a) and/or (5) under any acylating condition was unsuccessful, the reaction pathway on the formation of (4a) and/or (5) remains yet to be investigated.

This one-step synthesis of 3-carboxy-1,6-naphthyridin-4-one structure, which is analogous to nalidixic acid[8], was applied to the preparation of the compound (4c) for pharmacological testing.

Acylation of the N-ethyl-benzyl ester (1d), prepared from benzyl acetoacetate and ethylamine, with two molar amount of nicotinoyl chloride afforded (4b) in 23 % yield, which was then readily debenzylated in the presence of 10 % Pd-C to afford the carboxylic acid (4c) in 73 % yield.

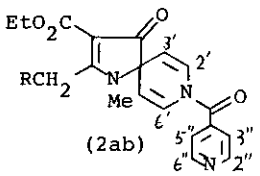
As mentioned above, acylation of (1a) with isonicotinoyl or nicotinoyl chloride proceeded to give the C-acylated products predominantly, while similar acylation of the enamine (6a), which was prepared from ethyl 2-oxocyclohexylcarboxylate and benzylamine, with the corresponding acid chloride afforded the N-acylated product (6b)[9] or (6c)[10] as a sole product in 95 and 84 % yields respectively. Prolonged acylation of (6b) with benzoyl chloride for 8 h. afforded the spirane (7)[11] in 75 % yield which then underwent ring cleavage to give the enamide (8)[12] upon hydrolysis with KOH. As in the case of (1c), attempted cyclization of the enamide (6c) under various acylating conditions was unsuccessful.

In conclusion, these results mentioned here and in the previous paper[1] made clear that isonicotinoyl and nicotinoyl chlorides were found to undergo acylation



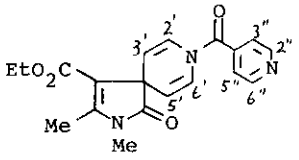
(1a-d)

| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| a | Me | H | Et |
| b | Me | isonicotinoyl | Et |
| c | Me | nicotinoyl | Et |
| d | Et | H | $CH_2Ph$ |

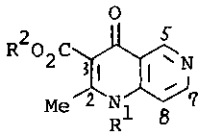


(2ab)

| | R |
|---|---|
| a | H |
| b | isonicotinoyl |

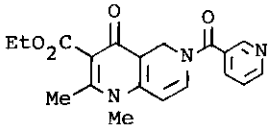


(3)

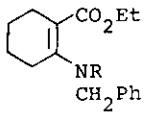


(4a-c)

| | $R^1$ | $R^2$ |
|---|---|---|
| a | Me | Et |
| b | Et | $CH_2Ph$ |
| c | Et | H |

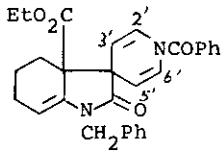


(5)

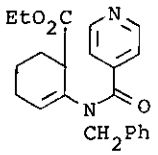


(6a-c)

| | R |
|---|---|
| a | H |
| b | isonicotinoyl |
| c | nicotinoyl |



(7)



(8)

of enamines to afford either the N-acylated or the C-acylated product depending on the structure of the enamine.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. T. Naito, O. Miyata, and I. Ninomiya, J. C. S. Chem. Commun., 1979, 517.
2. S. A. Glickman and A. C. Cope, J. Am. Chem. Soc., 1945, 67, 1017.
3. MS m/z: 353 ($M^+$). IR ($CHCl_3$) $cm^{-1}$: 1670, 1525. NMR ($CDCl_3$) $\delta$: 8.83 (2H, m, 2"- and 6"-H) (double primed numbers refer to the isonicotinoyl group), 4.80 (2H, d, J=8Hz, 3'- and 5'-H), 4.27 (2H, q, J=8Hz, $OCH_2CH_3$), 3.03 (3H, s, NMe), 2.63 (3H, s, C=C-Me), and 1.33 (3H, t, J=8Hz, $OCH_2CH_3$).

4. MS m/z: 458 ($M^+$). IR ($CHCl_3$) $cm^{-1}$: 1700, 1670, 1535. NMR ($CDCl_3$) $\delta$: 5.13 (2H, d, J=8Hz, 3'- and 5'-H), 5.07 (2H, s, $CH_2CO$), 4.33 (2H, q, J=8Hz, $OC\underline{H}_2CH_3$), 3.13 (3H, s, NMe), and 1.30 (3H, t, J=8Hz, $OCH_2C\underline{H}_3$).
5. MS m/z: 353 ($M^{+)}$. IR ($CHCl_3$) $cm^{-1}$: 1730, 1720, 1690, 1670, 1630. NMR ($CDCl_3$) $\delta$: 8.90 (2H, d-like, J=5Hz, 2"- and 6"-H), 7.50 (2H, d-like, J=5Hz, 3"- and 5"-H), 7.20 (2H, very br., 2'- and 6'-H), 4.93 (2H, br.d, J=9Hz, 3'- and 5'-H), 4.33 (2H, q, J=8Hz, $OC\underline{H}_2CH_3$), 3.27 (3H, s, NMe), 2.57 (3H, s, C=C-Me), and 1.30 (3H, t, J=8Hz, $OCH_2C\underline{H}_3$).
6. MS m/z: 246 ($M^+$). IR ($CHCl_3$) $cm^{-1}$: 1720, 1665, 1605. NMR ($CDCl_3$) $\delta$: 9.50 (1H, s, 5-H), 8.63 (1H, d, J=6Hz, 7-H), 7.50 (1H, d, J=6Hz, 8-H), 4.50 (2H, q, J=7Hz, $OC\underline{H}_2CH_3$), 3.67 (3H, s, NMe), 2.57 (3H, s, 2-Me),and 1.47 (3H, t, J=7Hz, $OCH_2C\underline{H}_3$).
7. MS m/z: 353 ($M^+$). IR ($CHCl_3$) $cm^{-1}$: 1710, 1650, 1600, 1580. NMR ($CDCl_3$) $\delta$: 8.80 (1H, d, J=2Hz, 2'-H), 8.73 (1H, dd, J=5 and 2Hz, 6'-H), 7.83 (1H, dt, J=8 and 2Hz, 4'-H), 7.37 (1H, dd, J=8 and 5Hz, 5'-H), 6.87 (1H, br.d, J=8Hz, 7-H), 5.73 (1H, d, J=8Hz, 8-H), 4.87 (2H, s, 5-$H_2$), 4.37 (2H, q, J=7Hz, $OC\underline{H}_2CH_3$), 3.57 (3H, s, NMe), 2.43 (3H, s, 2-Me), and 1.40 (3H, t, J=7Hz, $OCH_2C\underline{H}_3$).
8. W. W. Paudler and T. J. Kress, in " Advances in Heterocyclic Chemistry ", ed. A. R. Katritzky and A. J. Boulton, Academic Press, New York and London, 1970, vol. 11, p 123.
9. MS m/z: 364 ($M^+$). IR ($CHCl_3$) $cm^{-1}$: 1705, 1640. NMR ($CDCl_3$) $\delta$: 8.70 (2H,d, J=6Hz, 2- and 6-H), 5.47 and 4.30 (2H, ABq, J=14Hz, $C\underline{H}_2Ph$), 4.20 (2H, q, J=7Hz $OC\underline{H}_2CH_3$), and 1.30 (3H, t, J=7Hz, $OCH_2C\underline{H}_3$).
10. MS m/z: 364 ($M^+$). IR ($CHCl_3$) $cm^{-1}$: 1707, 1645. NMR ($CDCl_3$) $\delta$: 8.77 (1H, d, J=2Hz, 2-H), 8.57 (1H, dd, J=5 and 2Hz, 6-H), 7.87 (1H, dt, J=8 and 2Hz, 4-H), 5.40 and 4.30 (2H, ABq, J=14Hz, $C\underline{H}_2Ph$), 4.13 (2H, q, J=7Hz, $OC\underline{H}_2CH_3$), and 1.27 (3H, t, J=7Hz, $OCH_2C\underline{H}_3$).
11. MS m/z: 468 ($M^+$). IR ($CHCl_3$) $cm^{-1}$: 1720, 1675. NMR ($CDCl_3$) $\delta$: 5.23 (1H, m, CH=C), 5.10-4.70 (2H, m, 3'- and 5'-H), 4.87 (2H, s, $C\underline{H}_2Ph$), 4.23 (2H, q, J=7Hz, $OC\underline{H}_2CH_3$), and 1.20 (3H, t, J=7Hz, $OCH_2C\underline{H}_3$).
12. IR ($CHCl_3$) $cm^{-1}$: 1725, 1640. NMR ($CDCl_3$) $\delta$: 5.47 (1H, m, CH=C), 5.10 and 4.67 (2H, ABq, J=15Hz, $C\underline{H}_2Ph$), 4.20 (2H, q, J=7Hz, $OC\underline{H}_2CH_3$), 3.07 (1H, m, COCH-C=C), and 1.23 (3H, t, J=7Hz, $OCH_2C\underline{H}_3$).

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