A CONVENIENT SYNTHESIS OF ETHYL-β-DIOXOHYDROPYRIDINYL, ETHYL-β-DIHYDRODIOXOPYRIDO[3,2-c]PYRIDAZINYL AND ETHYL-β-OXOPYRANYLACRYLATE DERIVATIVES

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Abstract- A variety of pyridine, pyrido[3,2-c]pyridazine and pyran derivatives was synthesized from the enamino-nitrile derivative diethyl 3-amino-2-cyano-2-pentenedioate (1) as a starting material.

Polyfunctional nitriles are highly reactive reagents that have been extensively used in heterocyclic synthesis[1-3]. In the course of our investigations on the reactions of activated nitriles[4-7] for developing simple, new and efficient procedures for the synthesis of heterocycles, we report here a new synthesis of polyfunctional pyridine, pyrido[3,2-c]pyridazine and pyran derivatives starting with diethyl 3-amino-2-cyano-2-pentenedioate (1)[8].

Thus boiling of 1 (0.01 mole) in pyridine (50 ml) for 4 h (TLC monitoring) yielded a mixture of prodcuts which is separated by column chromatography on silica gel using ethyl acetate / methanol (19/1) as an eluent to give a major colourless product (56% yield) of molecular formula $C_{16}H_{16}N_4O_6$ (M^+=360) together with three other fractions. The structure of the major product could be formulated as 2 based on elemental analysis and spectral data. Structure 2 is corresponding to condensation of two molecules of 1 with elimination of two molecules of ethanol. Trials to identify the three other fractions were unsuccessful.

Coupling of 2 (0.01 mole) with arene diazonium chlorides afforded 3a-c which were readily cyclised on refluxing (2 h) in acetic acid (30 ml) - hydrochloric acid (2 ml) mixture via ethanol elimination to the pyrido[3,2-c]pyridazine derivatives 4a-c.

Condensation of the hydrazide 5 (0.01 mole) which is readily obtained[9] from 2 with an equimolar amount of acetylacetone in refluxing ethanol (30 ml) for 3 h in the presence of a catalytic amount of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (1 ml) afforded the oxopyran derivative 6 (M^+=262). The structure of 6 was based on elemental analysis and spectral data (cf. Tables 1 and 2). The formation of 6 is assumed to proceed via the sequence demonstrated in Chart 1.

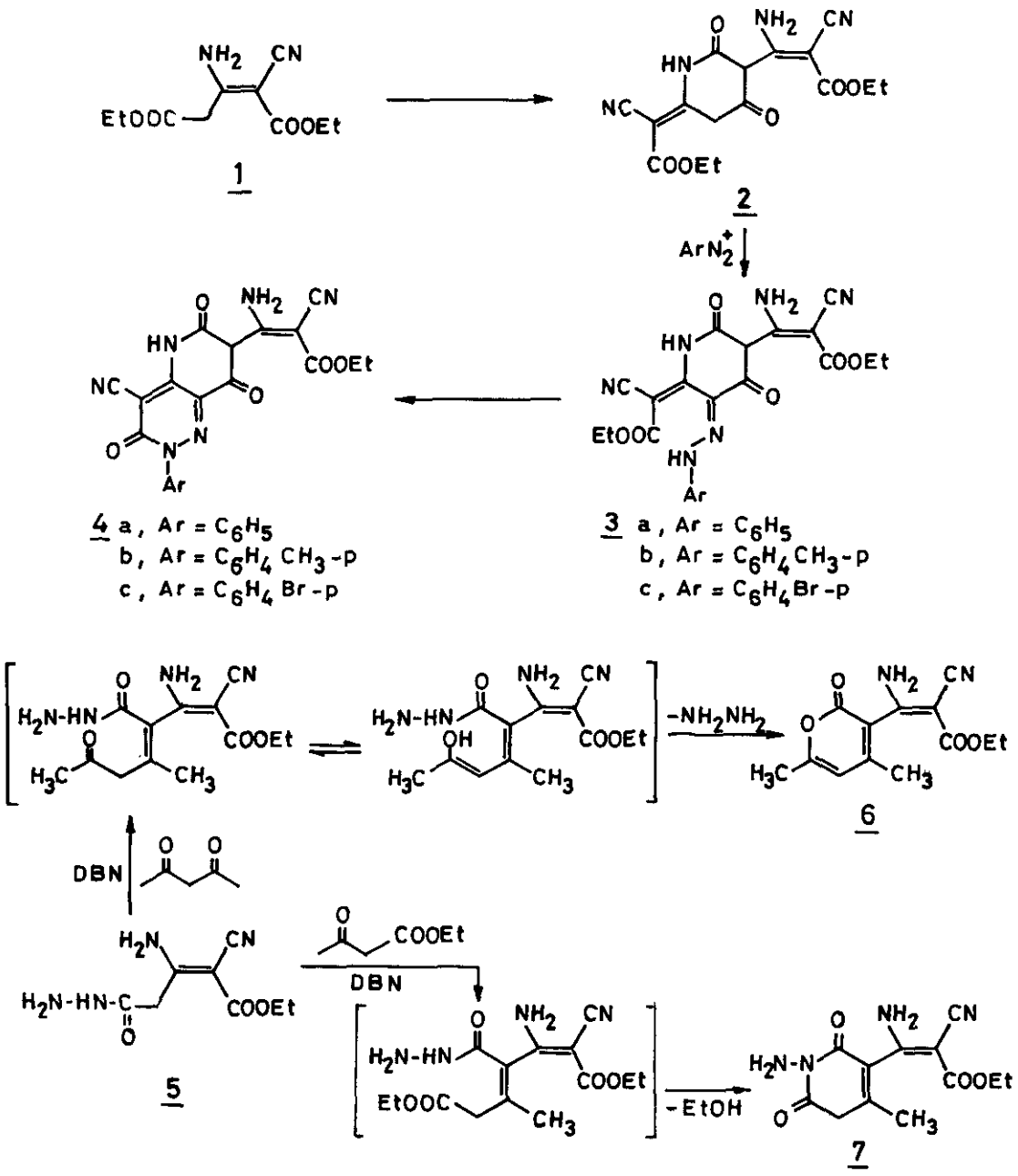
1
2
3 a, Ar = C6H5
b, Ar = C6H4CH3-p
c, Ar = C6H4Br-p
4 a, Ar = C6H5
b, Ar = C6H4CH3-p
c, Ar = C6H4Br-p
-NH2NH2
6
DBN
5
DBN
-EtOH
7

Chart 1

On the other hand, condensation of 5 (0.01 mole) with ethyl acetoacetate (0.01 mole) under similar conditions gave the pyridone derivative 7 (M^+=278) (cf. Chart 1).

The structures of the newly synthesized derivatives were established on the basis of analytical and spectroscopic data (Tables 1 and 2) and a variety of new heterocycles becomes now available. The biological activity of the products is now undertaken.

Table 1. List of the newly synthesized compounds.

Compound*	Mp. (°C)	Yield (%)	Mol. Formula	C % Calculated (Found)	H % Calculated (Found)	N % Calculated (Found)
2	179	56	$C_{16}H_{16}N_4O_6$	53.33 (53.20)	4.44 (4.20)	15.55 (15.70)
3a	241	75	$C_{22}H_{20}N_6O_6$	56.89 (57.10)	4.31 (4.30)	18.10 (18.20)
3b	202	80	$C_{23}H_{22}N_6O_6$	57.75 (57.80)	4.60 (4.50)	17.57 (17.30)
3c	189	72	$C_{22}H_{19}N_6O_6Br$	48.62 (48.80)	3.50 (3.40)	15.46 (15.50)
4a	196	85	$C_{20}H_{14}N_6O_5$	57.41 (57.30)	3.35 (3.40)	20.09 (20.10)
4b	300	79	$C_{21}H_{16}N_6O_5$	58.33 (58.40)	3.70 (3.60)	19.44 (19.60)
4c	207	81	$C_{20}H_{13}N_6O_5Br$	48.28 (48.30)	2.61 (2.70)	16.90 (16.80)
6	210	85	$C_{13}H_{14}N_2O_4$	59.54 (59.60)	5.34 (5.20)	10.68 (10.80)
7	257	68	$C_{12}H_{14}N_4O_4$	51.79 (51.90)	5.03 (5.10)	20.14 (20.30)

*All compounds are crystallized from ethanol except 3b, 6 and 7 which were crystallized from dioxan.

Table 2. Ir and ^{1}H nmr data of compounds 2, 3a, 4a, 6, and 7

Compound	Ir [cm^{-1}] Selected bands	^{1}H Nmr (δ ppm) [DMSO-d_6]
2	3395, 3380, 3320 (NH_2 and NH); 2225 2210 (two CN); 1760, 1750 (two ester CO); 1690, 1680 (ring CO); 1620 (C=N); 1600 (C=C).	1.3 (t, J=7 Hz, 6H, two ester CH_3); 1.5 (s, 3H, piperidone protons); 4.1 (q, J=7 Hz, 4H, two ester CH_2); 6.7 (s, 2H, NH_2); 8.5 (s, 1H, NH).
3a	3380 - 3250 (NH_2 and NH); 2220, 2200 two CN); 1765, 1750 (two ester CO); 1680, 1665 (ring CO); 1620 (C=N); 1600 (C=C).	1.3 (t, J=7 Hz, 6H, two ester CH_3); 1.4 (s, 1H, piperidone-H); 4.2 (q, J=7 Hz, 4H, two ester CH_2); 6.5 (s, 2H, NH_2); 7.3 - 8.1 (m, 7H, C_6H_5 and two NH).
4a	3450 - 3250 (NH_2 and NH); 2225 (CN); 1760 (ester CO); 1690, 1680, 1660 (ring CO); 1625 (C=N); 1610 (C=C).	1.1 (t, J=7 Hz, 3H, ester CH_3); 1.4 (s, 1H, piperidone-H); 4.1 (q, J=7 Hz, 2H, ester CH_2); 5.2 (s, 2H, NH_2); 7.2 - 7.8 (m, 6H, C_6H_5 and NH).
6	3400, 3300 (NH_2); 2210 (CN); 1770 (ester CO); 1695 (ring CO); 1620 (C=N); 1600 (C=C).	1.2 (t, J=7 Hz, 3H, ester CH_3); 2.4 (s, 3H, CH_3); 2.8 (s, 3H, CH_3); 4.2 (q, J=7 Hz, 2H, ester CH_2); 6.9 (s, 1H, pyran-H); 7.6 (s, 2H, NH_2).
7	3390 - 3300 (NH_2); 2210 (CN); 1770 (ester CO); 1680, 1670 (ring CO); 1625 (C=N); 1600 (C=C).	1.1 (t, J=7 Hz, 3H, ester CH_3); 1.4 (s, 2H, pyridone-H3); 2.7 (s, 3H, CH_3); 4.1 (q, J=7 Hz, 2H, ester CH_2); 5.4 (s, br, 4H, two NH_2).

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REFERENCES

1. H. Junek, Monatsh. Chem., 1963, 94, 192.
2. M. H. Elnagdi, M. R. H. Elmoghayar, D. H. Fleita, E. M. Hafez, and S. M. Fahmy, J. Org. Chem., 1967, 41, 3781.
3. K. Gewald and U. Hain, Synthesis, 1984, 62.
4. F. M. Abdel Galil, B. Y. Riad, S. M. Sherif, and M. H. Elnagdi, Chem. Lett., 1982, 1123.
5. F. M. Abdel Galil, S. M. Sherif, M. M. Sallam, and M. H. Elnagdi, Liebigs Ann. Chem., 1986, 1639.
6. F. M. Abdel Galil and M. H. Elnagdi, Liebigs Ann. Chem., 1987, 477.
7. F. M. Abdel Galil and A. O. Abdelhamid, Sulfur Lett., 1987, 6, 155.
8. *Prepared after the procedure described by* H. Junek and F. Frosch, Z. Naturforsch., 1971, 26b, 1124.
9. S. M. Fahmy, N. Abed, and R. M. Mohareb, Synthesis, 1982, 490.

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