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PREPARATION OF SUBSTITUTED PYRIDIN-2-ONES BY RING CLOSURE OF ACYLATED AMINOAZABUTADIENES

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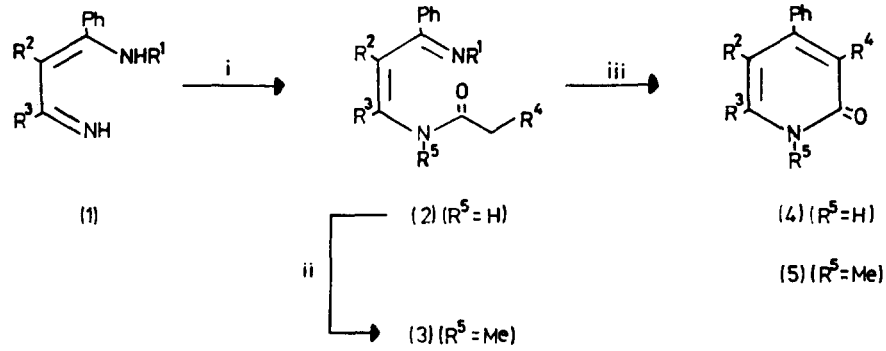
Summary: A facile and regioselective synthesis of pyridin-2-ones from acylated aminoazabutadienes is described.

The pyridin-2(1H)-one skeleton comprises the backbone of a number of natural products[1]. Though, pyridin-2(1H)-ones with electron-withdrawing groups are easily available, few general methods exist for preparing substituted, non-functionalized 2-pyridones[2,3,4]. Recently, Overman[4] reported an elegant synthesis of disubstituted pyridin-2(1H)-ones with alkyl or aryl groups at C-3 and C-6 by thermal rearrangement of propargylic pseudoureas; in some instances, the procedure suffers from low yields and by-product formation[4,5].

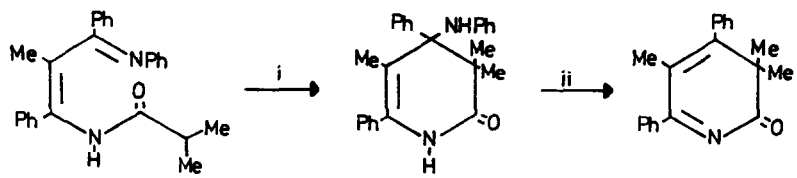
We report here that the regioselective preparation of substituted pyridin-2-ones is easily achieved by a new aldol-type ring closure reaction of the easy-to-make aminoazabutadienes (1)[6]. (Scheme 1).

Thus, treatment of compounds (2) (R^5=H), obtained by acylation of (1)[7], with LDA (2.5 eq.) at -78°C followed by stirring at room temperature for 12 h resulted in the formation of pyridones (4) in excellent yields[8]. (Table I). Moreover, N-alkylated 2-pyridone (5) was exclusively formed (77% from (2a)) if, prior to the ring closure step, (2a) was reacted with BuLi (1.2 eq.) and quenched with MeI to furnish (3) (90%; m.p. 110-112°C)[9]. (Scheme 1, Table I).



Scheme 1. Reagents: i, $ClCOCH_2R^4$, THF-pyridine, 25°C, 8 h.; ii, (a) BuLi (1.2eq.), THF, 0°C; (b) MeI, 0°C ⟶ 25°C, 12 h.; iii, LDA (2.5 eq. for (2) or 1.2 eq. for (3)), -78°C ⟶ 25°C, 12 h..

This reaction was then extended to the synthesis of the pyridin-2(3H)-one structure, which is rarely found in the literature[10]. (Scheme 2). Accordingly, the amide (6) (m.p. 160-162°C), prepared from (1) and isobutyryl chloride (CH_2Cl_2/Et_3N, 12 h, 95%), was allowed to react with LDA as above to give the addition compound (7)[11] (90%, m.p. 114-116°C); vacuum distillation of (7) (10^{-4} mm Hg, 170°C) produced quantitatively the pyridin-2-one (8)[11,12].



(6) (7) (8)

Scheme 2.Reagents: i, LDA (2.5 eq.), -78°C ⟶ 25°C, 24 h.; ii, Vacuum distillation.

Table I. *Pyridin-2(1H)-ones (4) and (5) from amide derivatives (2) and (3).*

Compound	R^2	R^3	R^4	R^5	*Yield(%)*[a]	*m.p.(°C)*[b]
(4a)	H	Ph	H	H	90	198-200
(4b)	Me	Ph	H	H	94	223-226
(4c)	Me	c-C_6H_{11}	Me	H	89	224-226
(4d)	Cl	p-MeC_6H_4	H	H	90	235-237
(4e)	Me	Ph	Ph	H	83	135-138
(4f)	CH_2=$CHCH_2$	p-MeC_6H_4	H	H	90	285-287
(5)	H	Ph	H	Me	85	oil

[a] *All reactions were carried out in a 0.02-0.03 molar scale.*
[b] *Compounds (4) were recrystallized from hexane-chloroform; compound (5) was purified by column chromatography (SiO_2, hexane-ether, 1:3).*

In conclusion, we have shown that this new ring-closure strategy becomes a very efficient route towards the regioselective synthesis of different types of pyridin-2-ones. Furthermore, the simplicity of the procedure and the availability of the materials used is also noteworthy.

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8.- Compound (4f): IR (KBr) 2970, 1660 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 2.4(3H,s), 3.0(2H,d J 5.4 Hz). 4.6(1H,dd, J 17.2 Hz, J 1.6 Hz), 4.8(1H,dd, J 10.2 Hz, J 1.6 Hz), 5.5(1H,m), 6.9(1H,s), 7.1-7.7(9H,m) and 11.3(1H,NH,s broad) ppm; δ_C (75 Mz; $CDCl_3$) 21.24(q), 31.78(t), 113.69(t), 115.53(s), 119.54(d), 127.91-131.40(m), 139.24(s), 139.38(s), 145.41(s), 157.36(s) and 162.94(s) ppm; Ms(70 eV) m/e 301 (M^+).

9.- Alkylation of substituted pyridin-2(1H)-ones gives in most instances mixtures of N- and O-alkylated products: A.R. Katritzky and C.W. Rees, `Comprehensive Heterocyclic Chemistry´, Pergamon Press, Oxford, 1984, Vol. 2.

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11.- Compound (7): IR (KBr) 3200, 1650 cm^{-1}; δ_H (80 MHz; $CDCl_3$) 1.2(3H,s), 1.3(3H,s), 1.8(3H,s), 4.2(1H,NH,s broad), 6.6-7.8(16H,m) ppm; δ_C (20 Mz; $CDCl_3$) 14.90(q), 24.10(q), 25.20(q), 39.24(s), 75.50(s), 117.40(d), 120.00(d), 124.87-128.91(m), 138.10(s), 141.41(s), 143.75(s) and 173.81(s) ppm; Ms(70eV) m/e 382 (M^+).
Compound (8): IR (CH_2Cl_2) 1703, 1628 cm^{-1}; δ_H (80 MHz; $CDCl_3$) 1.1(6H,s), 1.6(3H,s), 7.0-7.6(10H,m) ppm; δ_C (20 MHz; $CDCl_3$) 16.11(q), 22.83(q), 43.87(s), 123.10(s), 125.00-130.20(m), 136.50(s), 137.42(s), 160.90(s), 172.60(s) and 189.12(s) ppm; Ms(70eV) m/e 289 (M^+). Compound (8) is air sensitive and must be handled under nitrogen.

12.- All new compounds (2), (3), (4), (5), (6), (7) and (8) gave satisfactory spectroscopic and analytical data.

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