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[1,2,3]TRIAZOLO[1,5-a]PYRIDINE - A SYNTHON FOR 6-SUBSTITUTED PYRIDINE-2-CARBOXALDEHYDES

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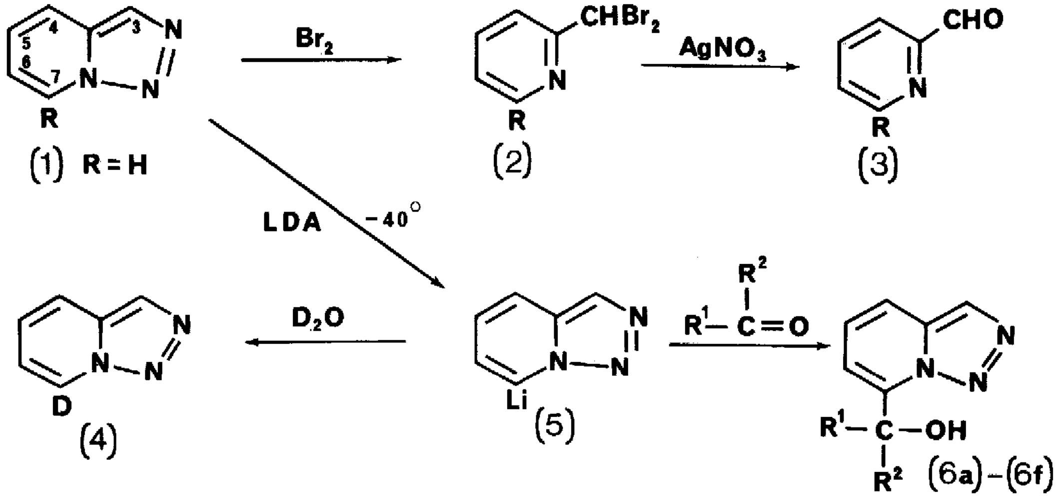
Abstract [1,2,3]Triazolo[1,5-a]pyridine (1) is lithiated in position 7; the lithio derivative is used to synthesize triazolopyridinyl alcohols (6) which can be converted into 6-substituted pyridine-2-aldehydes (3).

We have reported elsewhere[1] that [1,2,3]triazolo[1,5-a]pyridine (1) reacts with bromine to give high yield of 2-dibromomethylpyridine (2, R=H), and we have found that this compound can be hydrolysed in excellent yield by aqueous alcoholic silver nitrate to pyridine-2-aldehyde (3, R=H), thus reversing the usual synthesis of triazolopyridine.[2] We have now found that triazolopyridine (1) can be lithiated at -40° by lithium diisopropylamide (LDA) in ether; quenching with D_2O gave 7-deuteriotriazolopyridine (4). The position of deuteriation and hence of lithiation is established by the ^1H n.m.r. spectrum of the 7-deuterio compound which lacks the characteristic downfield broadened doublet at δ 8.75 p.p.m. of triazolopyridine. The two series of experiments open the way to a general synthesis of 6-substituted pyridine-2-aldehydes, and we record here some preliminary examples



Treatment of the lithium derivative (5) with aldehydes or ketones gave the alcohols (6a)-(6f), collected in Table 1. The yields in some cases are modest, but we have optimized only the production of (6c) and (6e), which were used to demonstrate the further conversion into the pyridine-2-aldehydes. As an example of the experimental procedure we report the synthesis of alcohol (6c). A solution of n-butyllithium (14.52 ml, 1.16M, in hexane) was added to diisopropylamine (2.6 ml), at -40°, under dry nitrogen. An ethereal solution (80 ml) of triazolopyridine (1) (2g.) was added to the stirred solution, and stirring continued (6 h.) during which a red colour developed. Addition of anisaldehyde (2.05 ml, 2.29 g.) caused the colour to change to yellow; the mixture was stirred overnight at room temperature. Hydrolysis with ammonium chloride in 0.880 ammonia gave a yellow solid, which on filtration was shown to be almost pure alcohol (6c), (2.77 g. 69%), m.p. 171-172° (benzene). (Found: C, 65.75; H, 5.05; N, 16.75. $C_{14}H_{13}N_3O$ requires C, 65.85; H, 5.15; N, 16.45%). ^{1}H n.m.r. ($CDCl_3$), δ 3.82 (3H, s, OCH_3), 4.49 (1H, d, J 4.6 Hz, OH), 6.5 (1H, d, J 4.6 Hz, CHOH), 6.73 (1H, br d, J 7.1 Hz, H6), 6.93 (2H, d, J 8.9 Hz, H2', 6'), 7.24 (1H, q, J 7.1 and 8.8 Hz), 7.49 (2H, d, J 8.9 Hz, H3', 5'), 7.7 (1H, d of d, J 8.8 and 1.1 Hz, H4), and 8.12 (1H, s, H3) p.p.m. Analysis figures, and full spectral details are available for all the alcohols (6); for most, medium pressure chromatography on silica was used for purification.

TABLE 1 : Alcohols (6)$^{+}$ from lithiotriazolopyridine

	R^1	R^2	% yield	M.p. or B.p.
(6a)	H	n-C_7H_{15}	30	Unstable to distillation
(6b)	H	C_6H_5	30	123.5 - 124.6°
(6c)	H	4-$CH_3OC_6H_4$	69	171 - 172°
(6d)	$CH_2CH_2CH_2CH_2CH_2$		25	100°
(6e)	C_6H_5	C_6H_5	52	186.5 - 187.5°
(6f)	CH_3	4-pyridyl	40	125 - 126°

Two examples illustrate the conversion of the alcohols (6) into 6-substituted pyridine-2-aldehydes (3). Bromine (1.25 g.) in dichloromethane (25 ml.) was added slowly to a stirred solution of alcohol (6e) (2 g.) in dichloromethane (100 ml.); nitrogen evolution was observed. After addition stirring was continued (1 h.). The solution was shaken with saturated $NaHCO_3$ solution, dried, and evaporated to give almost pure dibromomethylpyridine (2, R = $(C_6H_5)_2C(OH)$-), (2.19 g., 76%), m.p. 118-120° (EtOH). (Found: C, 53.0; H, 3.5; N, 3.35. $C_{19}H_{15}Br_2NO$ requires C, 52.7; H, 3.5; N, 3.25%) ^{1}H n.m.r. δ 5.8 (1H, s, OH), 6.6 (1H, s, $CHBr_2$), 6.9-7.4 (12H, m), and 7.7 2H, m) p.p.m. Compound (6c) gave the dibromomethylpyridine (2, R = 4-$CH_3OC_6H_4CH(OH)$-) as an oil, in virtually quantitative yield. The dibromomethylpyridines were hydrolysed by aqueous alcoholic silver nitrate (20 min., water bath) to give the pyridine aldehydes (3, R = 4-$CH_3OC_6H_4CH(OH)$-, and R = $(C_6H_5)_2C(OH)$-) in 78% and 100% yield; both were characterized as DNP derivatives, m.p. 189-192° and 197-199° respectively.$^{+}$

We are examining the reaction of the lithiotriazolopyridine (5) with a variety of other electrophiles, to give a wide range of 2,6-disubstituted pyridines.

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References

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$^{+}$ Analytical and spectral data are available for all new compounds.

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