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NUCLEOPHILIC SUBSTITUTIONS ON BROMOTRIAZOLOPYRIDINES - AN IMPROVED ROUTE TO 2,6-DISUBSTITUTED PYRIDINES AND TO 1,3-DISUBSTITUTED ISOQUINOLINES

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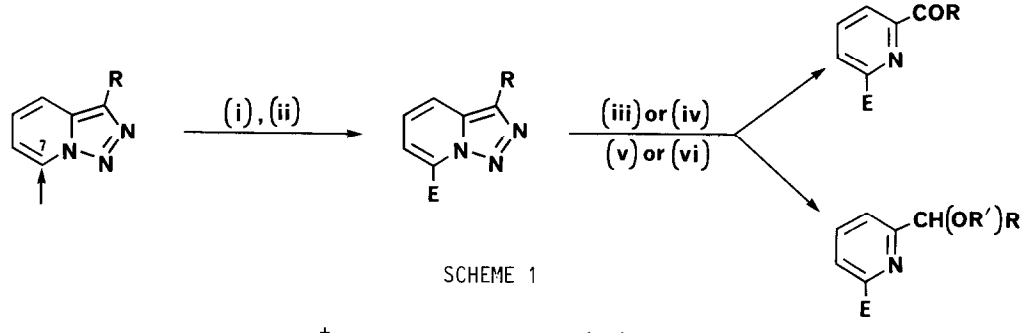
Summary. A regiospecific synthesis of 2,6-disubstituted pyridines and of 1,3-disubstituted isoquinolines is described.

We have described regiospecific lithiation of triazolopyridines[1-3], triazoloquinolines[4], and triazoloisoquinolines[5]. Subsequent reaction of these lithio derivatives with electrophiles, followed by opening of the five membered ring with loss of dinitrogen provided syntheses of 2,6-disubstituted pyridines, 2,3-disubstituted quinolines, or 1,3-disubstituted isoquinolines. The sequence is exemplified in Scheme 1.

The synthesis would be considerably improved if nucleophilic substitution could also be achieved on the triazolopyridines, for example via the introduction of a bromine substituent into positions 5 or 7 on triazolopyridine (1). We have now achieved this transformation, and thus, for example, have direct access by nucleophiles to position 3 in isoquinoline.



SCHEME 1

(i) LDA (ii) E^+ (iii) SeO_2 (iv) Br_2, AgOH
(v) H^+, H_2O (R' = H) (vi) AcOH, boil (R' = Ac).

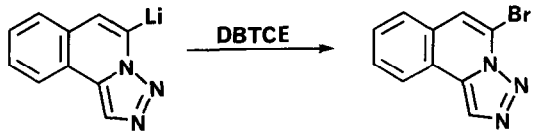
We have previously attempted to prepare 7-bromotriazolopyridine by treatment of the 7-lithio derivative (1) with bromine at -40 °C but even at this low temperature ring opening was so rapid that only 6-bromo-2-dibromomethylpyridine could be isolated. Introduction of a substituent into position 3 of triazolopyridine slows the ring opening sufficiently to allow the isolation from lithio compounds (2) and (4) of the corresponding

bromo compounds (3) and (5) in 5% and 10% yields respectively. Since trial experiments showed that the bromine substituents in compounds (3) and (5) were readily displaced by methoxide in methanol, the synthesis is clearly viable if the yield of bromide can be increased. Of the reagents tried the best was dibromotetrachloroethane (DBTCE), which reacted with the lithio derivative (2) in toluene as solvent to give the bromo compound (3) m.p. 34-36 °C in 70-80% yield. Similar treatment of 7-lithiotriazolopyridine (1) with DBTCE gave 60-70% yields of bromide (6), m.p. 95-95.5 °C, and 5-lithiotriazoloisoquinoline (7) gave 5-bromotriazoloisoquinoline (8), m.p. 161-162 °C, in 65% yield. The bromide (3) is the easiest to handle and has been treated with a range of nucleophiles to give 7-substituted-3-methyltriazolopyridines (9) in good to excellent yield. The parent bromide (6) also reacts readily but the 7-substituted derivatives are less stable and we are developing procedures to convert them directly into pyridines. The bromotriazoloisoquinoline (8) gave 5-methoxytriazoloisoquinoline (10) (50%, not optimized). Representative reactions are grouped in Table 1.

(1) R = H
(2) R = Me
(4) R = $CONEt_2$

(3) R = Me
(5) R = $CONEt_2$
(6) R = H

	R	Nu
(9) a	H	OMe
b	Me	OMe
c	Me	$OC_6H_4OCH_3$-4
d	Me	SPh
e	Me	Piperidine
f	Me	$NHNH_2$
g	$CONEt_2$	OMe



(7) (8)

We have reported four reagents for the conversion of triazolopyridines into pyridines;[6] aqueous sulphuric acid or glacial acetic acid gave 2-hydroxymethyl- or 2-acetoxymethyl-pyridines (11), while selenium dioxide, or bromine (followed by base) gave pyridine-2-carboxaldehydes or ketones (12). We have applied a selection of these procedures to our new triazolopyridines with success, and have demonstrated that our regiospecific synthesis of 2,6-disubstituted pyridines is now completely general. Oxidative ring opening of 5-methoxytriazoloisoquinoline (10) using selenium dioxide in xylene gave 3-methoxy-isoquinoline-1-carboxaldehyde (13) in 85% yield, and we are now concentrating on the production of many new 1,3-disubstituted isoquinolines. Ring opening reactions are grouped in Table 2.

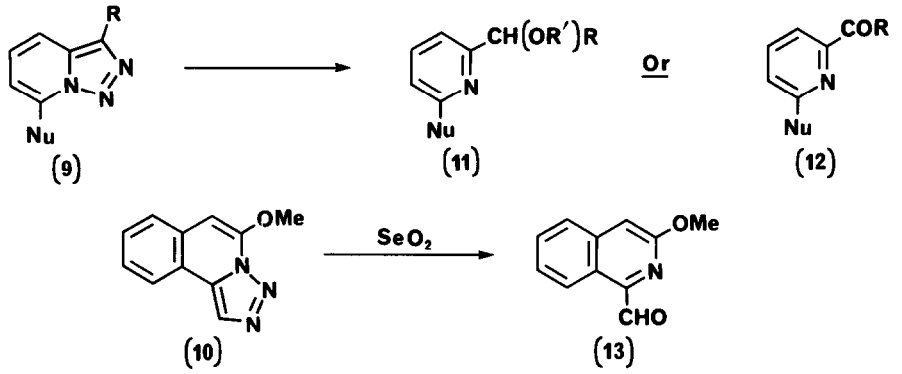


TABLE 1: Nucleophilic Substitution Products from Bromotriazolopyridines

Bromide	Product	Nucleophile	Solvent/Temp. °C	Time(h)	Yield %	M.p. °C
6	9a	MeO^-	MeOH, 60	24	95[a]	-
3	9b	MeO^-	MeOH, 60	19	>90	34-36
3	9c	$4\text{-}MeOC_6H_4O^-$	DMF, 95	15	90	128-128.5
3	9d	PhS^-	DMF, 95	17	95	118-119
3	9e	Piperidine	EtOH, 78	72	60	101-103
3	9f	Hydrazine	EtOH, 78	100	65	154-155
5	9g	MeO^-	MeOH, 60	10	92	125-127
8	10	MeO^-	MeOH, 60	20	50	167-169

[a] Estimated by n.m.r.; decomposed on chromatography to give compound 11, R=R'=H, Nu=OMe

TABLE 2: Selected Ring Opening Reactions on Substituted Triazolopyridines

Compound	Reagent	Temp.(°C)	Time(h)	Product (%)	Refs.
9a	H_2SO_4 (2N)	95	2	11, R=R'=H, Nu=OMe (80)	7,8
9b	SeO_2, chlorobenzene	135	1	12, R=Me, Nu=OMe (60)	8
9c	SeO_2, chlorobenzene	135	1	12, R=Me, $Nu=OC_6H_4OCH_3$-4 (70)	- [b]
9e	Glacial AcOH	118	2	11, R=Me, R'=Ac, Nu=piperidinyl (75)	- [c]
10	SeO_2, xylene	138	1	13, (85), m.p. 79-81°	9

[b] M.p. 75-76 °C [c] b.p. 135-140°/0.05 mm Hg.

Satisfactory analyses have been obtained for all new compounds.

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