Tetrahedron Vol. 40, No. 2, pp. 311 to 314, 1984
Printed in Great Britain.

0040-4020/84 $3.00 + .00

STUDIES ON $S_{RN}1$ REACTIONS—9[1]

A NEW ACCESS TO THE ISOQUINOLINE RING SYSTEM

RENÉ BEUGELMANS, JACQUELINE CHASTANET and GEORGES ROUSSI*
Institut de Chimie des Substances Naturelles, C.N.R.S. F-91190-Gif sur Yvette, France

(*Received in France* 25 *September* 1982)

Abstract—The $S_{RN}1$ reaction between *o*-halogeno-benzylamines and enolates derived from a series of ketones and aldehydes affords 1, 2 dihydro-isoquinolines from which are obtained (i) the isoquinoline derivatives, either spontaneously or by treatment on Pd–C and (ii) the 1, 2, 3, 4 tetrahydro-isoquinoline derivatives after sodium borohydride reduction.

The extension of the $S_{RN}1$ reaction to aryl halides bearing a function Y adjacent to the leaving group X has already provided a straightforward access to a variety of heterocyclic ring systems. Treatment of substrates ArXY with enolates derived from ketones or aldehydes led to the primary $S_{RN}1$ product [A] which most often underwent a spontaneous cyclisation to give indoles,[2-4] azaindoles,[4,5] benzofuranes,[6] isocarbostyrils,[7,8] and isocoumarones[7] (Scheme 1).

A new synthesis of the isoquinoline ring system based on the above scheme starting from *o*-halogeno–benzylamines is presented.

RESULTS AND DISCUSSION

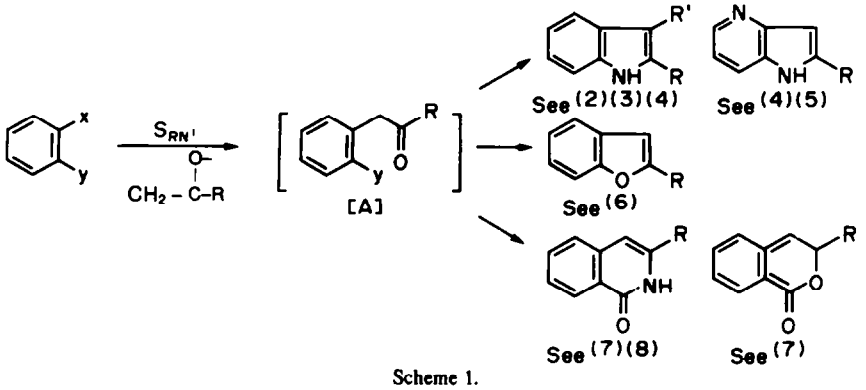
The *o*-chloro-benzylamine **1** or the *o*-bromo-benzylamine **2** treated with the acetone derived enolate (a) under $S_{RN}1$ conditions[9] was found to undergo a rather sluggish reaction (1 h) giving a mixture from which 3-methylisoquinoline **4a** and 3 - methyl - 4 - hydroxy-isoquinoline **5a** (**4a**/**5a** = 1/3) were isolated in low yield (25%). When using the iodide which is known to be a better leaving group than Cl^- or Br^- in the aromatic $S_{RN}1$ process, reaction between **3** and the enolate (a) was very fast (5′) and afforded a high yield (80%) of the same mixture of products in a similar ratio. The *o*-iodo-benzylamine **3** was therefore chosen for reacting with other enolates. The reaction of the isopropyl or *t*-butyl derived enolates (**b**) or (**c**) with **3** were found to be identical with the reaction of the enolate (**a**) and to give **4b** + **5b** (80%) or **4c** + **5c** (~100%).

In the absence of photostimulation when **3** was treated with enolate (**a**) or (**c**) no reaction occured and the starting material **3** was recovered unchanged even after a long period of time, providing support for an $S_{RN}1$ mechanism (steps 1–4) (Scheme 3).

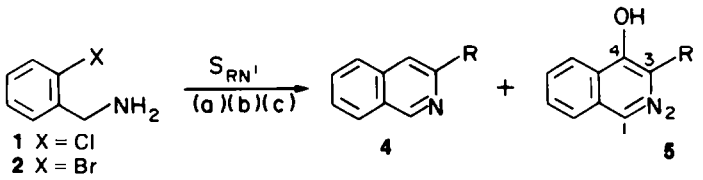
The $S_{RN}1$ process gives rise to the $S_{RN}1$ primary product [A] which cannot be isolated since it undergoes a spontaneous cyclisation (possibly in the reaction medium) to give, via the α-amino alcohol [B], the 2-unsubstituted 1, 2 dihydro-isoquinoline [C] (Scheme 4). A model $S_{RN}1$ reaction carried out with an appropriately N-protected *o*-iodobenzylamine **6** and the enolate (**a**) gave **7** together with some amount of **8** whose origin lies in the commonly encountered competitive reduction of the aryl-radical[II]. The primary $S_{RN}1$ product **7** was fully characterized and after treatment under acidic conditions was cyclised to the 2-methoxycarbonyl, 3 - methyl, 1, 2 - dihydroisoquinoline **9** analogous to [C]. As anticipated **9**, being substituted on position 2 was stable. No trace of other derivatives (4-hydroxy compound for instance) was detected in this sequence. The compound **11** too is stable under the $S_{RN}1$ conditions but, **7** lost its protecting group during acidic treatment to give a mixture of **4a** + **5a**. The experiment carried out on **10** supports the structure postulated for [A] and along with the experiments carried out on **7** indicates clearly that (i) [A] and [C] are involved as intermediates leading to **4a, b** (ii) **5a, b** also derived from [A] were not formed during the course of the $S_{RN}1$ reaction (eqns 1–4) but *subsequently*.

Synthetic scope

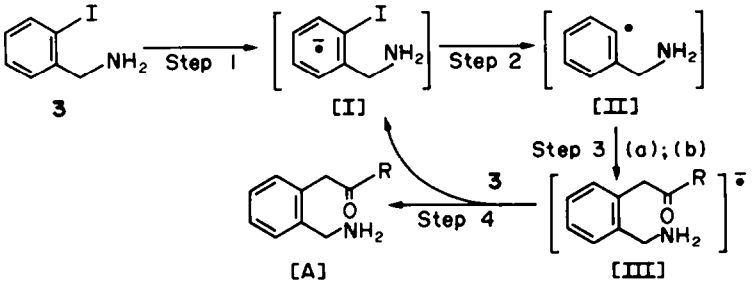
The S_{RN} reaction is thus very efficient for building [A] (the combined yields of **4a, b, c** + **5a, b, c** amount to 80%) and therefore it was worth trying to control the reactivity of the sequence [A] [B] [C]. Very little information is available concerning 2-unsubstituted 1, 2 dihydroisoquinolines and we had to rely upon analogies with the reactivity



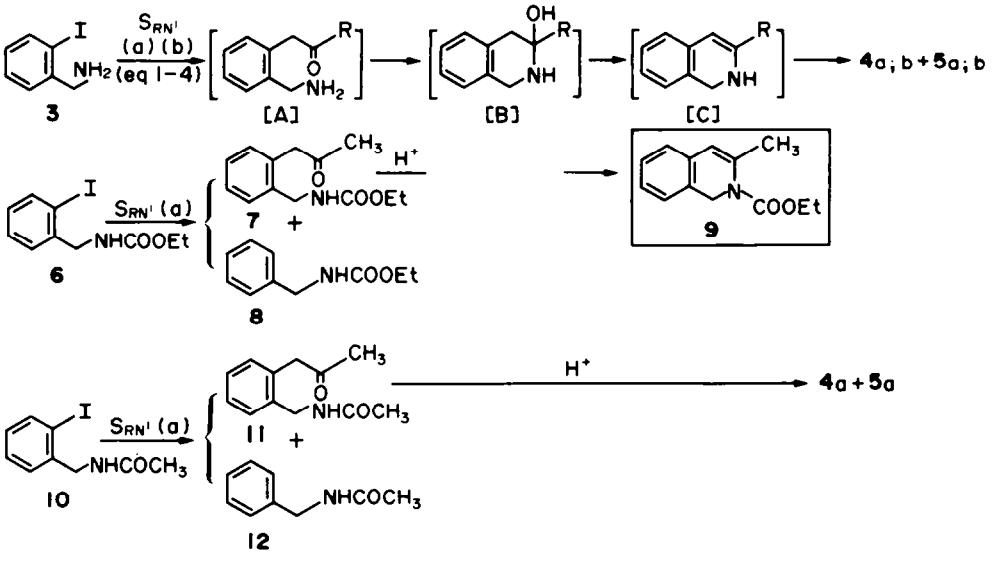
Scheme 1.



Scheme 2. The $S_{RN}1$ reaction of *o*-halobenzylamines.



Scheme 3. The formation of [A], the primary product of the $S_{RN}1$ reaction (eqns 1 – 4).



Scheme 4. Characterization of [A] and [C].

of the more stable, and therefore better documented, 2-substituted 1, 2-dihydroisoquinolines.

We anticipated that, among some of the well documented reactions of the 2-substituted 1, 2-dihydroisoquinolines,[10–12] reduction and oxidation could possibly be carried out on [C].

(a) *The reduction of* [*C*]: *access to 3-substituted 1, 2, 3, 4 tetra-hydroisoquinolines.* The crude product of the reaction between **3** and the enolates (**a**, **b** and **d**), after removal of the ammonia under an argon stream, was dissolved in acidic methanol and treated with sodium borohydride in excess (Scheme 5).

High yields of the expected tetrahydroisoquinolines **13**, **14**, **15**, were thus obtained as the unique products.

(b) *The oxidation of* [*C*]: *access to 3-substituted isoquinoline derivatives.* In the reaction of **3** with the enolate (**a**) by bubbling air before or after quenching the $S_{RN}1$ reaction or by manganese dioxide treatment of the crude product, a dimeric compound, to which the structure of a 4, 4'-di-isoquinoline **17** has been ascribed†, was obtained together with various amounts of **5a**.

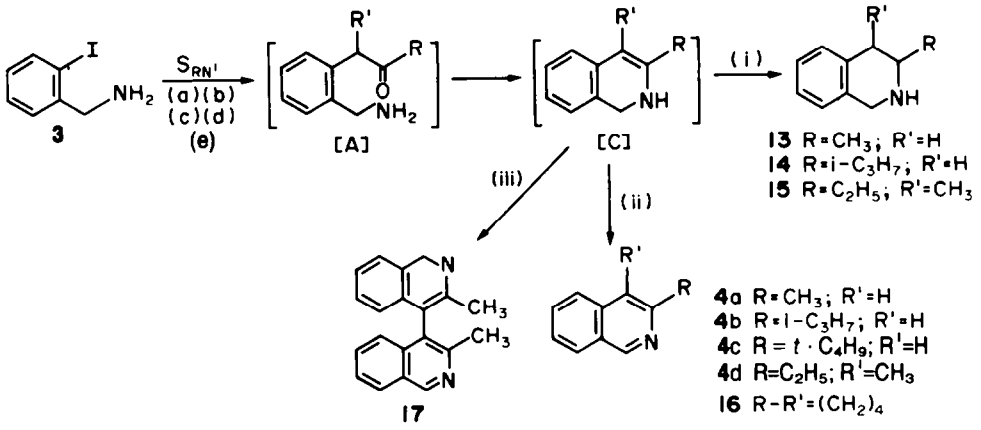
We found that it was nevertheless possible to drive the $S_{RN}1$ reaction toward the exclusive formation of the 3-substituted isoquinoline by treating the crude product of the reaction between **3** and various enolates (**a**, **b**, **d**, **e**) with Pd–C, a reaction reported for the dehydrogenation of 1, 2, 3, 4-tetrahydro - and 3, 4 - dihydroisoquinolines. Thus **4a**, **b**, **c**, **d** and the phenanthridine **16** were obtained in high yield.

The $S_{RN}1$ reaction as an access to 3-substituted 4-hydroxyisoquinoline. Although none of the results reported (experiments on **7**, **9**, **11**; oxidation) indicated a pathway by which **5a**, **b**, **c** were formed, the compounds nevertheless are obtained in appreciable yields by a method simpler than some others hitherto reported.[11]

The $S_{RN}1$ reaction as an access to 3-functionalized

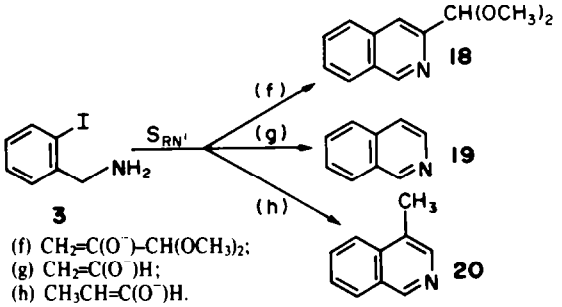
†The position 4 where the "extra" hydroxyl of **5a**, **b**, **c** is located is also the site of the coupling which gave rise to **17**.

Note added in proof: Dr. F. McCapra has suggested that the 4-hydroperoxides are possible precursors of **5** a,b,c, by processes analogous to those encountered when 3-indolenyl hydroperoxides are treated with K Ot-But (F. McCapra and Y. C. Chang, *Chem. Commun* 522 (1966)).



Scheme 5. Reduction and oxidation of [C]. Synthesis of 3- substituted 1, 2, 3, 4 tetrahydro isoquinolines or of 3-substituted isoquinoline derivatives.

(a) $CH_2{=}C(O^-){-}CH_3$; (b) $CH_2{=}C(O^-){-}i{-}C_3H_7$; (c) $CH_2{=}C(O^-){-}t{-}C_4H_9$; (d) $CH_3{-}CH{=}C(O^-){-}C_2H_5$; (e) $\bigcirc\!\!-O^-$ (i) $BH_4Na/MeOH/H^+$; (ii) Palladized charcoal; (iii) air bubbling followed by work up under alkaline conditions or MnO_2 oxidation of the crude product.



Scheme 6.

isoquinolines and to 4-alkyl isoquinolines. The dimethoxy pyruvaldehyde derived anion (**f**), the use of which was introduced for the synthesis of the 2-formylindole[3] appeared to be a suitable nucleophile when opposed to **3** giving **18** in reasonable yield. Although no other product than **18** was detected, we observed that a cleaner product was obtained after treatment of the crude product by Pd–C (Scheme 6).

The aldehyde derived anions are suitable nucleophiles for indole synthesis via $S_{RN}1$ reactions[3] and here the acetaldehyde derived anion (**g**), opposed to **3** was found to give the parent isoquinoline **19** while the anion (**h**) derived from propionaldehyde gave the 4-methylisoquinoline **20**. This last reaction is of interest since it constitutes a new entry to the 4-alkylated isoquinolines which compares favorably with other methods,[13] including that based upon the alkylation of the 2-methyl-1, 2-dihydro-isoquinoline.[14]

CONCLUSION

The $S_{RN}1$ reaction extented to *o*-halogeno-benzylamines provides, via the primary reaction product [**A**] a ready access to the 1, 2 - dihydro - isoquinoline [**C**] which has been easily manipulated to give the isoquinoline or the 1, 2, 3, 4 - tetrahydro - isoquinoline ring systems. This new method is more flexible and more direct than other classical methods giving access to 1, 2 - dihydro-isoquinolines.[10–12] On the other hand, the scope of the $S_{RN}1$ reaction is enlarged by the hitherto unreported ability of *o*-halogeno–benzylamine to be reactive substrates.

EXPERIMENTAL

M.ps were determined on a Reichert apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer spectrometer and UV spectra (EtOH) with a Jobin et Yvon instrument. ^1H NMR spectra ($CDCl_3$; TMS as the internal standard) were recorded on a Varian T60 or a Perkin–Elmer R12 instrument. Mass spectra were obtained with AEI MS9 spectrograph. Purification was achieved either by column chromatography or by preparative thin-layer plates (Kieselgel 60 GF 254 Merck) eluted with mixture of CH_2Cl_2–MeOH in various proportions. Commercially available *o*-iodobenzylamine was purchased from Interchim (Montluçon, France).

General procedure for $S_{RN}1$ reactions. Dry ammonia (100 ml) was condensed under argon in a 3-necked flask fitted with a dry ice condenser and rubber taps. Freshly sublimed t-BuOK (448 mg, 4 mmole), the carbonyl compound (4 mmole) and then *o*-iodobenzylamine (233 mg, 1 mmole) were added. A pronounced purple coloration appeared soon after and disappeared quickly after starting irradiation with a 100 W medium pressure mercury lamp (Hanau Q81). The reaction was monitored by TLC and at the end, after removing the condenser the ammonia was evaporated under a dry argon stream in a well ventilated hood, leaving the crude product.

3.Methyl-isoquinoline **4a** *and 4-hydroxy - 3 - methyl-isoquinoline* **5a**. The crude product obtained from the reaction carried out with the acetone derived anion (**a**) (irradiation time 5') was hydrolyzed with NH_4Cl aq. Work-up (CH_2Cl_2) and preparative TLC yielded: **4a** (33 mg, 23%), m.p. (ether) 68° (lit.[15] 68°]; δ (^1H) 3.15 (3H, s) 7.40–8.1 (5H, m) 9.2 (1H, s); *m/e* 143 (M^+); **5a** (95 mg, 60%) m.p. (CH_2Cl_2/hexane) 179° [lit.[16] 180°];IR (KBr) 3400, 1625, 1580 cm-1; δ (^1H) 2.6. (3H, s) 7.2.–8.4 (5H, m), 8.6. (1H, s); *m/e* 159 (M^+).

3-i-Propyl-isoquinoline **4b** *and 4-hydroxy-3-i-propyl-isoquinoline* **5b**. The crude product obtained with the anion (**b**) derived from 3-methyl-2-butanone (irradiation time 5') treated as described afforded quantitatively, after similar work up a crude $S_{RN}1$ product where **4b** and **5b** 40/60 were characterized by NMR. No attempt was made for purification (*vide infra*: **4b**).

3 - t - Butyl-isoquinoline **4c** *and 4 - hydroxy - 3 - t - butyl-isoquinoline* **5c**. The crude product obtained with the anion (**c**) derived from 3, 3 - dimethyl - 2 - butanone (irradiation time 5') treated as described afforded after similar work up and purification: **4c** (oil) (35 mg, 20%); Picrate m.p. (EtOH) 160°

(Found; C, 54.79; H, 4.28; N, 13.24; O, 26.87 $C_{13}H_{25}NO$ requires: C, 55.07; H, 4.37; N, 13.52; O, 27.03%); δ (^1H) 1.45 (9H, s), 7.3–8.2 (5H, m); 9.22 (1H, s); *m/e* 185 (M^+).

Compound **5c** isolated as a crystalline but rather unstable product (75 mg, 60%); m.p. (ether/pentane) 168° Found: C, 76.79; H, 7.48; N, 6.93; O, 8.16 $C_{13}H_{15}NO$ requires: C, 77.60; H, 7.46; N, 6.96; O, 7.96%); δ (^1H) (CD_3OD) 1.25 (9H, s) 7.05–8.1 (4H, m), 8.25 (1H, b, s); *m/e* 201, 114 (M^+), $C_{13}H_{15}NO$ requires 201, 270.

2 - *Oxypropyl - benzylamine - methoxy - carbonyl* **7**. This compound (130 mg, 58%) was obtained after work up and preparative TLC purification of the crude product resulting from the reaction of **6** [m.p. (ether/hexane) 74°] with enolate (**a**) (irradiation time 50') m.p. (ether hexane) 62°; (Found C, 64.91; H, 7.04; N, 6.51; O, 21.57 $C_{12}H_{15}NO_3$ requires C, 65.14; H, 6.83; N, 6.33; O, 21.69%); δ (^1H) 2.15 (3H, s), 3.6 (3H, s), 3.75 (2H, s) 4.22 (2H, d), 5.2–5.6 (1H, b. s), 7.0–7.4 (4H, m); *m/e* 221 (M^+), 202, 162. Benzyl - amino - methyl ester **8** (19 mg, 11%) was a side product.

Acid hydrolysis of **7**: *formation of* 3 - *methoxycarbonyl* - 1, 2 *dihydroisoquinoline* **9**. A soln of **7** (30 mg, 0.13 mmol) in benzene (2 ml) containing *p*-toluenesulfonic acid (10 mg) was prepared under argon and heated at 80° in a sealed tube for 5 hr. Work up and preparative TLC yielded **9** (11 mg, 41%). IR 3000, 1700, 1630, 1200, 920 cm^{-1}; δ (^1H) 2.28 (3H, s), 3.73 (3H, s) 4.7 (2H, s), 5.97 (1H, b s), 6.8–7.4 (4H, m); *m/e* 203, 0946 (M^+), $C_{12}H_{13}NO_2$ requires: 203, 0946; 188; 156; $\lambda_{max} = 278$; $\epsilon = 6600$.

2-*Oxypropyl-benzylacetamide* **11**. This compound (62 mg, 30%) was obtained after work-up and preparative TLC of the crude product resulting from the reaction of **10** m.p. (CH_2Cl_2) 134°, [lit.[17] 134°–135° with the enolate (**a**) (irradiation time 40'). δ (^1H) 1.95 (3H, s), 2.15 (3H, s), 3.82 (2H, s) 4.32 (3H, d) 5.5–6.1 (1H, b s), 7.1–7.6 (4H, m). Benzylacetamide **12** (43 mg, 28%) was a side product of this reaction.

Acid hydrolysis of **11**. A soln of **11** (41 mg, 0.2 mmol) in HCl 4N (1 ml), prepared under argon was heated in a sealed tube for 4 hr at 100°. After work up, a mixture of **4a** and **5a** [**4a**/**5a** = 40/60 as determined by NMR]was obtained.

3-*Methyl*-1, 2, 3, 4-*tetrahydroisoquinoline* **13**. The product obtained from the reaction of **3** with enolate (**a**) (irradiation time 10') dissolved in acidic MeOH (20 ml) and treated with a large excess of $NaBH_4$ gave **13** (133 mg, 90%) almost pure [lit.[18]]. δ (^1H) 1.25 (3H, d), 1.9 (1H exchanged with D_2O), 2.4–3.5 (3H, m), 4.05 (2H, b s), 7.1 (4H, b s); *m/e* 147 (M^+).

3 - *i* - *Propyl* - 1, 2, 3, 4 - *tetrahydroisoquinoline* **14**. The product obtained from the reaction of **3** with enolate (**b**) (irradiation time 6') reduced with $NaBH_4$ gave a mixture of **14** and **4b** (~10%). Purification on silica gel plates yielded pure **14**; oil; (135 mg 60%). δ(^1H) 1.05 (6H, d), 2.7. (3H, b.s.), 4.1 (2H, s), 7.12 (4H, s) *m/e* 175 (M^+).

N-*Sulfonamide*. **14** in pyridine soln, treated with *p*-toluenesulfonyl chloride gave, after work up and evaporation of EtOH- a crystalline derivative m.p. = 117° [lit.[19] 117°]. Recrystallisation from ether gave crystals m.p. 140°.

3 - *Ethyl* - 4 - *methyl* - 1, 2, 3, 4-*tetrahydroisoquinoline* **15**. Under similar conditions, the product obtained from **3** and the enolate (**d**) afforded a mixture of *cis*- and *trans* - 3 - ethyl - 4 - methyl - tetrahydroisoquinoline (yield > 90% as determined by NMR with internal standard), which was purified by preparative TLC (143 mg, 83%). δ(^1H), 1.0–1.8 (8H, m), 1.95 (1H, s, exchanges with D_2O), 2.4–3.1. (2H, m), 4.0 (2H, s), 6.6–7.3 (4H, m); *m/e* 175 (M^+), 160, 146, 118 117.

1, 2, 3, 4-*tetrahydrophenanthridine* **16**. The product obtained from the $S_{RN}1$ reaction of **3** and the cyclohexanone derived enolate (**e**) (irradiation time 20') was hydrolysed with a sat NH_4Cl soln. Work up and preparative TLC purification afforded **16** (82 mg, 43%), Picate m.p. (EtOH) 194–196° [lit.[20] 192–193°]; δ(^1H) 1.8.–2.2. (4H, m), 2.8 3.2 (4H, m), 7.0–7.9 (4H, m), 8.8 (1H, s); *m/e* 183 (M^+).

The one pot synthesis of 3-*methyl-isoquinoline* **4a**, 3-*i*-*propyl isoquinoline* **4b** *and* 3-*ethyl-4-methyl-isoquinoline* **4d**. The crude product obtained from the reaction of **3** with the enolates (**a**, **b**, **d** was dissolved in MeOH (20 ml) and refluxed (4 hr) with Pd–C 5%. Filtration and work-up gave **4a** (100% as determined by NMR with internal standard) identical with the compound obtained above: **4b** (100% as determined by NMR with internal standard; 94% after purification) (irradiation time 6'); δ(^1H) 1.3–1.4 (6H, d) 2.95–3.4 (1H, b. s.), 7.3–8.0 (6H, m); *m/e* 171 (M^+), 156 (M^+–15). Picrate m.p. (EtOH) 159° [lit[19] 159°]. **4d** (100% as determined by NMR with internal standard; oil 77% (132 mg) after purification) was obtained after a longer irradiation time (25'). Picrate m.p. (EtOH) 202° (Found; C, 53.87; H., 3.92; N. 13.96; O, 27.81; $C_{18}H_{16}N_4O_7$ requires; C, 54.00; H, 4.03; N, 13.99; O, 27.97%); δ (^1H), 1.3 (3H, t) 2.55 (3H, s), 3.02 (2H,q), 7.0–8 (4H, m), 9.22 (1H, b.s); *m/e* 171 (M^+).

4,4'-Di-(3-methyl-isoquinoline) **17**. The $S_{RN}1$ reaction of **3** and enolate (**a**) yielded after ammonia elimination under air atmosphere **4a** (27 mg, 18%) and 4, 4 - di - (3 - methyl-isoquinoline **17** (47 mg 32%); oil; δ^1 H,.2.32 (6H, s), 6.94–7.3 (2H, m) 7.4, 7.85 (4H, m), 7.9–8.4 (2H, m) 9.35 (2H, s); *m/e* 284, 1306 (M^+) $C_{20}H_{16}N_2$ requires: 284. 1313.

3-*Formyl-dimethyl-acetal-isoquinoline* **18**. The crude product of the $S_{RN}1$ reaction between **3** and the pyruvaldehyde-dimethyl-acetal derived anion (**f**) (irradiation time 15'), after work up and purification afforded **18** (78 mg, 38%); Picrate m.p. (EtOH) 138°. (Found C, 49.78; H, 3.80; N, 12.86; O, 33.19; $C_{18}H_{16}N_4O_9$ requires: C, 50.00; H, 3.73; N, 12.96; O, 33.30%); δ(^1H) 3.45 (6H, s), 5.6 (1H, s), 7.3–8.3 (5H, m), 9.3 (1H, s); *m/e* 202(M-1), 173, 172, 158.

Isoquinoline **19**. The $S_{RN}1$ reaction of **3** and the acetaldehyde derived enolate (**g**) according to the procedure described (irradiation time 10') gave after work up and preparative TLC the isoquinoline **19** (65 mg, 50%) and benzylamine (11 mg, 10%) both identical to authentic samples.

4-*Methyl-isoquinoline* **20**. Similarly **3** and the propionaldehyde derived enolate (**h**), after work up and preparative TLC, afforded **20** (34 mg, 30%); Picrate m.p. (EtOH) 202° [lit.[21] 202–203°]; δ(^1H) 2.6 (3H, s), 7.2–8.2 (5H, m), 9.0 (1H, s); *m/e* 143 (M^+) 115.

REFERENCES

[1]Preliminary results: R. Beugelmans, J. Chastanet and G. Roussi, *Tetrahedron Letters* 2313 (1982).

[2]R. Beugelmans and G. Roussi, *J. Chem. Soc. Chem. Commun.* 950 (1979).

[3]R. Beugelmans and G. Roussi, *Tetrahedron* **37**, supl. n° 1, 393 (1981).

[4]R. R. Bard and J. -F. Bunnett, *J. Org. Chem.* **45**, 1546 (1980).

[5]R. Beugelmans, B. Boudet and L. Quintero, *Tetrahedron Letters* 1943 (1980).

[6]R. Beugelmans and H. Ginsburg, *J. Chem. Soc. Chem. Commun.*, 508 (1980).

[7]R. Beugelmans and M. Bois-Choussy, *Synthesis* 729 (1981).

[8]R. Beugelmans, M. Bois-Choussy and H. Ginsburg, *J. Chem. Soc.* Perkin 1, 1149 (1982).

[9]J. -F. Bunnett, *Acc. Chem. Res.* **11**, 413 (1978).

[10]S. -F Dyke, *Advances in Heterocyclic Chemistry* (Edited by A. R. Katritsky and A. J. Boulton) Vol. **14**, p. 279. Academic Press New York (1973).

[11]S. -F. Dyke, *Rodd's Chemistry of Carbon Compounds* (Edited by S. Coffey) 2nd Edn, Vol. IV F, p. 427. Elsevier, Amsterdam (1976).

[12]S. -F. Dyke and R. G. Kinsman, *The Chemistry of Heterocyclic Compounds* Vol. **38**, Part 1, *Isoquinolines* (Edited by G. Grethe). Wiley New York (1981).

[13]J. M. Bobbitt, *Advances in Heterocyclic Chemistry* (Edited by A. R. Katritsky and A. J. Boulton) Vol. **15**, p. 99. Academic Press, New York (1973).

[14]M. Sainsbury, D. W. Brown, S. -F. Dyke, R. D. J. Clipperton and W. R. Tonkyn, *Tetrahedron* **26**, 2239 (1970).

[15]S. Gabriel and A. Neumann, *Ber. Dtsch Chem. Bis.* **25**, 3563 (1892).

[16]S. A. Harris, T. J. Webb and K. Folkers, *J. Am. Chem. Soc.* **62**, 3198 (1940).

[17]T. Ukai, Y. Yamamoto, M. Yotsuzuka and F. Ichimura, *J. Pharm. Soc. Jap.* **76**, 657, *Chem Abstr*, **51**, 280 g (1957).

[18]L. S. Hegedus, G. F. Allen and E. L. Waterman, *J. Am. Chem. Soc.* **98**, 2674 (1976).

[19]L. Arsenijevic and V. Arsenijevic *Bull. Soc. Chem. Fr.* 3403 (1968).

[20]T. Masamune, M. Ohno, M. Koshi, S. Ohuchi and T. Iwadare, *J. Org. Chem.* **29**, 1420 (1964).

[21]E. Spath, F. Berger and Kuntera, *Ber. Dtsch. Chem. Bis.* **63**, 134 (1930).