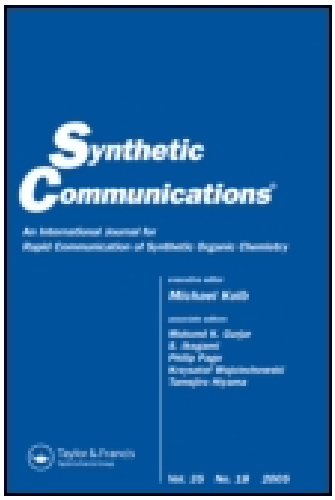

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REACTIVITY OF ETHYL 1,2,3,4-TETRAHYDRO-6,7-DIMETHOXY-1-ISOQUINOLYLIDENE ACETATE TOWARDS NITRILIMINES. SYNTHESIS OF PYRROLO[2,1-*a*]-5,6-DIHYDROISOQUINOLINE

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ABSTRACT

Hydrazonoyl halides **3** and **8** react with 3,4-dihydro-6,7-dimethoxyisoquinoline-1-methyleneethoxycarbonyl **2** to give ethyl 2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline-1-ylidene)-2-(*N*-phenyl-*N*′-benzylidene-hydrazine) acetate **7** and pyrrolo[2,1-*a*]5,6-dihydroisoquinoline **13** respectively. Structures of the new compounds were elucidated on the basis of elemental analysis, spectral data (IR, ^{1}H NMR, MS).

In continuation of our previous work on the use of isoquinoline derivatives for the synthesis of heterocyclic compounds.[1–3] I wish to report the synthesis of pyrrolo[2,1-*a*]dihydroisoquinoline derivatives. Such ring systems have a considerable pharmacological activities as cardiovascularly,[4] antiflammatory[5] and antidepressant.[6] Also, I study the effect of

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the presence of the carbonyl group in α-ketohydrazonoyl halide on the course of the reaction.

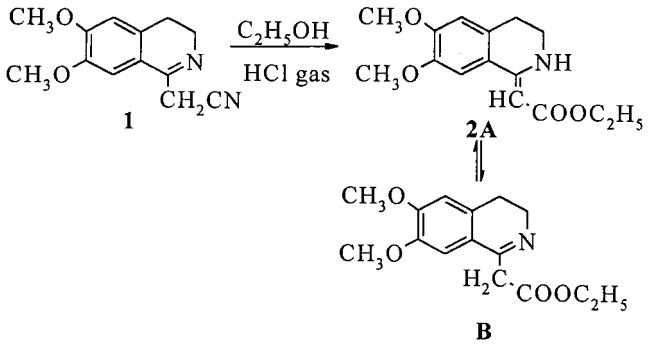
RESULTS AND DISCUSSION

The starting material **2** was prepared by esterification of **1** in absolute ethanol as previously described.[7] Its ^{1}H NMR spectrum confirmed the enamine form **2A** (Scheme 1). It shows signals at δ 1.5 (t, 3H), 2.8 (t, 2H), 3.4 (t, 2H), 3.8 (s, 3H), 3.9 (s, 3H), 4.2 (q, 2H), 5.0 (s, 1H), 6.7 (s, 1H), 7.1 (s, 1H), 9.0 (s, 1H, NH).

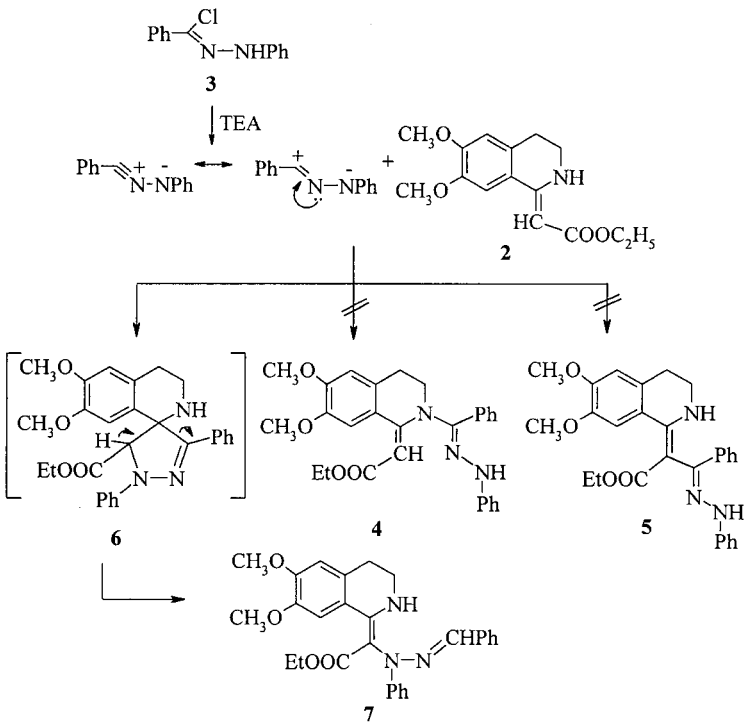
Reaction of 3,4-dihydro-6,7-dimethoxyisoquinoline-1-methyleneethoxycarbonyl **2** with diphenylnitrilimine, generated in situ by the reaction of triethylamine on the *N*-phenylbenzohydrazonoyl chloride **3** in refluxing chloroform, yielded a product whose elemental analysis was compatible with the amidrazone structure **4**, the hydrazone **5** or the rearranged product **7** resulting from the spiro compound **6** (Scheme 2).

Although amidrazone of type **4** is known to be stable[8–10] all attempts made to separate it from the reaction mixture were failed. The substitution product **5** was rejected on the basis of its ^{1}H NMR and IR spectrum. The IR spectrum of **5** reveals two NH stretching vibrations which not appear in the IR spectrum of the product. The structure of compound **7** was confirmed on the basis of ^{1}H NMR and ^{13}C NMR spectra. Thus ^{1}H NMR spectrum shows a signal at δ 8.1 corresponding to the methine CH-proton of the hydrazone moiety.[11,12]

Next, the effect of carbonyl group in α-ketohydrazonoyl halides on the course of their reaction with **2** was investigated. Treatment of **2**



Scheme 1.



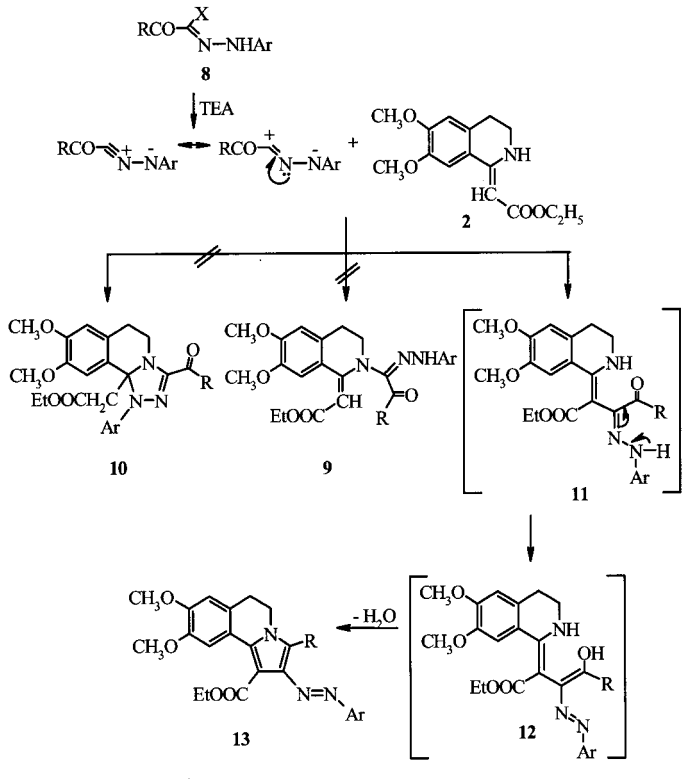
Scheme 2.

with α-ketohydrazonoyl halides **8** in refluxing chloroform in the presence of triethylamine leads to the formation of **13**. In all cases, only one product was formed as shown by TLC and ^{1}H NMR of the crude reaction mixture. The isolated products **13** gave satisfactory elemental analyses and spectroscopic data (IR, ^{1}H NMR, MS) for the proposed structures. For example, the IR spectra of all the products isolated from the reaction of **8** with **2** showed a characteristic carbonyl absorption band for ethoxycarbonyl group near 1700 cm^{-1}.

The ^{1}H NMR spectra of all compounds showed a triplet signal at δ 1.4 and quartet signal at δ 4.4 corresponds to ethoxycarbonyl group in **13**. The mass spectra of all compounds exhibit a molecular ion peak with high intensity. The electronic absorption spectra of the resulting products are characterised by four intense maxima at λ near 480, 410, 330 and 250 nm assignable to azo chromophore.[13]

Also, ^{13}C-NMR of compound **13a** taken as a typical example illustrates the signals that confirm the structure **13**. On the basis of the above

data, the products isolated from reaction of **8** with **2** were assigned structure **13** and not the amidrazone **9** or the cycloadduct **10**. The reaction pathway that seems to account for the formation of **13** from **8** and **2** is outlined in Scheme 3. It is proposed that the reaction involves initial nucleophilic substitution to give **11**, which cyclized via elimination of the elements of water to give **13**.



	R / Ar		R / Ar
a	CH_3 / C_6H_5	**e**	2-naphthyl / C_6H_5
b	CH_3 / 4-$CH_3C_6H_4$	**f**	2-naphthyl /4-$CH_3C_6H_4$
c	C_6H_5 / C_6H_5	**g**	2-theinyl / C_6H_5
d	C_6H_5 / 4-$CH_3C_6H_4$	**h**	2-theinyl / 4-$CH_3C_6H_4$

Scheme 3.

EXPERIMENTAL

Melting points were taken on a Gallenkamp apparatus and are uncorrected. Infrared spectra (KBr) were determined on a Pye Unicam SP-3000 infrared spectrophotometer. The NMR spectra in $CDCl_3$ were recorded on a Varian Gemini 200 instrument (^{1}H NMR 200 MHz) with TMS as the internal standard. Elemental analyses were carried out at the Microanalytical center, University of Cairo, Giza, Egypt. Hydrazonoyl halides **3**,[14] **8a,b**[15], **8c,d**[16], **8e,f**[17], **8g,h.**[18]

Synthesis of ethyl 2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline-1-ylidene)-2-(*N*-phenyl-*N*′-benzylidenehydrazine)acetate 7: To a solution of hydrazonoyl halide **3** (5 mmol) and 3,4-dihydro-6,7-dimethoxyisoquinoline-1-methyleneethoxycarbonyl **2** (1.38 g, 5 mmol) in chloroform (40 mL) was added triethylamine (1.4 mL, 10 mmol) at room temperature. The reaction mixture was refluxed for 6 h. The solvent was evaporated under reduced pressure and the residue was triturated with methanol (10 mL) where it solidified. The crude product was collected and crystallised from dimethylformamide-ethanol mixture to give the corresponding ethyl 2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline-1-ylidene)-2-(*N*-phenyl-*N*′-benzylidenehydrazine) acetate **7**. The compound prepared with its physical constants are given below. **7**: m.p. 170°C; 80% yield; ν_{max}/cm^{-1} (KBr) 1640 (C=O); δ_H ($CDCl_3$) 1.1 (t, $J = 7$Hz, 3H), 3.4 (m, 2H), 3.5 (s, 3H), 3.8 (s, 3H), 4.0 (m, 2H), 4.1 (q, $J = 7$Hz, 2H), 6.8 (s, 1H), 7.1 (s, 1H), 7.1–8.1 (m, 10H), 10.5 (s, 1H); ^{13}C ($CDCl_3$) (APT pulse sequence) δ 16.30, 31.10, 40.75, 57.47, 57.55, 61.14, 82.71, 112.054, 113.27, 115.02, 121.67, 122.71, 127.89, 129.37, 130.11, 131.25, 132.94, 141.91, 145.35, 147.13, 149.30, 152.82, 160.65, 172.0; *m*/*z* 471; (Found: C, 71.2; H, 5.9; N, 8.8. $C_{28}H_{29}N_3O_4$ requires C, 71.3; H, 6.1; N, 8.9%).

Synthesis of pyrrolo[2,1-*a*]-5,6-dihydroisoquinoline 13: These compounds were prepared by the same method described for the synthesis of **7** using hydrazonoyl halide **8** in place of **3** to give **13**. The compounds prepared with their physical constants are given below. **13a**: m.p. 187°C; 82% yield; ν_{max}/cm^{-1} (KBr) 1693 (C=O); δ_H ($CDCl_3$) 1.3 (t, $J = 7$ Hz, 3H), 2.6 (s, 3H), 3.0 (m, 2H), 3.9 (s, 3H), 4.0 (s, 3H), 4.0 (m, 2H), 4.3 (q, $J = 7$ Hz, 2H), 6.7 (s, 1H), 7.4 (s, 1H), 7.4–7.8 (m, 5H); ^{13}C ($CDCl_3$) (APT pulse sequence) δ 9.25, 14.14, 28.45, 40.72, 55.86, 55.92, 61.14, 108.14, 111.08, 122.08, 122.22, 125.15, 128.76, 128.99, 129.19, 133.46, 148.50, 148.65, 153.43, 168.96, 181.06; *m*/*z* 419; (Found: C, 68.8; H, 5.6; N, 9.8.$C_{24}H_{25}$ N_3O_4 requires C, 68.7; H, 5.9; N, 10.0%). **13b**: m.p. 188°C; 80% yield; ν_{max}/cm^{-1} (KBr) 1714 (C=O); δ_H ($CDCl_3$) 1.2 (t, $J = 7$Hz, 3H), 2.3 (s, 3H), 2.5 (s, 3H), 3.3 (m, 2H), 3.8 (s, 3H), 3.9 (s, 3H), 3.9 (m, 2H), 4.3 (q, $J = 7$Hz, 2H), 6.5 (s, 1H), 7.0 (s, 1H), 7.2–7.7 (m, 4H), *m*/*z*

433; (Found: C, 69.0; H, 6.1; N, 9.5. $C_{25}H_{27}N_3O_4$ requires C, 69.2; H, 6.2; N, 9.6%). **13c**: m.p. 214°C; 78% yield; ν_{max}/cm^{-1} (KBr) 1718 (C=O); δ_H ($CDCl_3$) 1.3 (t, $J=7$ Hz, 3H), 3.0 (m, 2H), 3.9 (s, 3H), 4.0 (s, 3H), 4.1 (m, 2H), 4.4 (q, $J=7$Hz, 2H), 6.7 (s, 1H), 7.3 (s, 1H), 7.3–7.7 (m, 10H); *m/z* 481; (Found: C, 72.6; H, 5.4; N, 8.5. $C_{29}H_{27}N_3O_4$ requires C, 72.3; H, 5.6; N, 8.7%). **13d**: m.p. 220°C; 81% yield; ν_{max}/cm^{-1} (KBr) 1710 (C=O); δ_H ($CDCl_3$) 1.4 (t, $J=7$ Hz, 3H), 2.4 (s, 3H), 3.0 (m, 2H), 3.9 (s, 3H), 4.0 (s, 3H), 4.0 (m, 2H), 4.4 (q, $J=7$Hz, 2H), 6.7 (s, 1H), 7.1 (s, 1H), 7.2–7.7 (m, 9H); *m/z* 495; (Found: C, 72.5; H, 5.6; N, 8.1. $C_{30}H_{29}N_3O_4$ requires C, 72.7; H, 5.8; N, 8.4%. **13e**: m.p. 271°C; 79% yield; ν_{max}/cm^{-1} 1708 (C=O); δ_H ($CDCl_3$) 1.3 (t, $J=7$Hz, 3H), 3.0 (m, 2H), 3.9 (s, 3H), 4.0 (s, 3H), 4.2 (m, 2H), 4.4 (q, $J=7$ Hz, 2H), 6.7 (s, 1H), 7.3 (s, 1H), 7.3–8.1 (m, 12H); *m/z* 531; (Found: C, 74.6; H, 5.6; N, 7.8. $C_{33}H_{29}N_3O_4$ requires C, 74.6; H, 5.5, N, 7.9%). **13f**: m.p. 218°C; 80% yield; ν_{max}/cm^{-1} (KBr) 1706 (C=O); δ_H ($CDCl_3$) 1.3 (t, $J=7$ Hz, 3H), 2.3 (s, 3H), 3.0 (m, 2H), 3.9 (s, 3H), 4.0 (s, 3H), 4.1 (m, 2H), 4.4 (q, $J=7$ Hz, 2H), 6.7 (s, 1H), 7.2 (s, 1H), 7.2–8.1 (m, 11H); *m/z* 545; (Found: C, 74.7; H, 5.6; N, 7.5. $C_{34}H_{31}N_3O_4$ requires 74.8; H, 5.6; N, 7.7%). **13g**: m.p. 159°C; 81% yield; ν_{max}/cm^{-1} (KBr) 1713 (C=O); δ_H ($CDCl_3$) 1.3 (t, $J=7$ Hz 3H), 3.0 (m, 2H), 3.9 (s, 3H), 4.0 (s, 3H), 4.2 (m, 2H), 4.4 (q, $J=7$ Hz, 2H), 6.7 (s, 1H), 7.2 (s, 1H), 7.2–7.8 (m, 8H), *m/z* 487; (Found: C, 66.6; H, 5.3; N, 8.6; S, 6.7. $C_{27}H_{25}N_3O_4S$ requires C, 66.5; H, 5.1; N, 8.6; S, 6.5%). **13h**: m.p. 210°C; 78% yield; ν_{max}/cm^{-1} (KBr) 1701 (C=O); δ_H ($CDCl_3$) 1.3 (t, $J=7$ Hz, 3H), 2.4 (s, 3H), 3.0 (m, 2H), 3.9 (s, 3H), 4.0 (s, 3H), 4.2 (m, 2H), 4.4 (q, $J=7$ Hz, 2H), 6.7 (s, 1H), 7.1 (s, 1H), 7.2–8.2 (m, 7H); *m/z* 501; (Found: C, 67.0; H, 5.1; N, 8.4; S, 6.1. $C_{28}H_{27}N_3O_4S$ requires C, 67.0; H, 5.3; N, 8.3; S, 6.3%).

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