Studies on 1,3-Dipolar Cycloaddition Reactions of Some Cycloimmonium Ylides

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1,3-Dipolar cycloaddition reactions of zwitterionic quinolinium and isoquinolinium ylides, generated in situ from their respective precursors, with acetylenic dipolarophiles led to the formation of benzoindolizine derivatives. The reaction presumably proceeds via intermediacy of nonaromatic primary adducts which on dehydrogenation afford aromatized benzoindolizines. The structures of resulting products have been confirmed by elemental analysis as well as by spectroscopic methods.

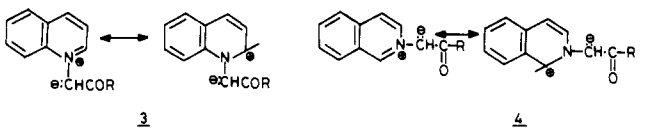
Our interest in cycloimmonium ylides for the synthesis of heterocyclic compounds by elimination of heteroaromatic rings via ylide bond cleavage (*1-3*) prompted us to carry out a different type of reaction for the synthesis of some new heterocyclic compounds in which the heteroaromatic ring remains intact in the final product. With the view of exploring this synthetic approach for such heterocyclic compounds, we have, therefore, carried out 1,3-dipolar reactions of some quinolinium and isoquinolinium ylides (see Scheme I) with acetylenic dipolarophiles. Though similar 1,3-dipolar cycloaddition reactions of some semistabilized and stabilized cycloimmonium ylides have been reported earlier (*4-7*) almost no attention has been paid to studying the reaction of carbonyl-stabilized quinolinium and isoquinolinium ylides toward acetylenic dipolarophiles after the only report of Henerick et al. (*8*).

In the present communication we report the synthesis of some new benzoindolizine derivatives (see Table I) by the reaction of acetylenic dipolarophiles with carbonyl-stabilized quinolinium and isoquinolinium ylides, generated in situ from their respective bromide salts.

Experimental Section

Melting points were determined on a Gallenkamp apparatus and were uncorrected. A Beckman DU spectrophotometer was used to record UV spectra with chloroform as a reference. The IR spectra were recorded on a Perkin-Elmer spectrophotometer using KBr. NMR spectra ($CDCl_3$) were run on a Varian A-60 spectrometer with Me_4Si: as an internal standard, and chemical shifts are expressed in δ values. Analytical samples were purified by column chromatography over neutral alumina, and

Scheme I



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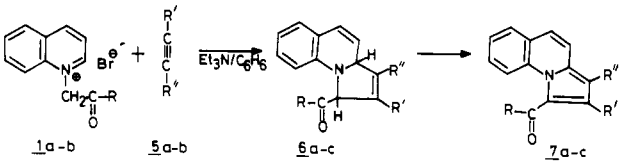
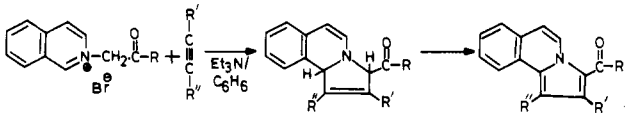
Scheme II



1a-b 5a-b 6a-c 7a-c

Scheme III



2a-d 5a-b 8a-g 9a-g

purity was checked by thin-layer chromatography (TLC). (See Table II for spectral data.)

Preparation of Benzoindolizine Derivatives (7a-c) via Quinolinium Ylides. Triethylamine (0.7 cm^3) was added to a stirred solution of phenacylquinolinium bromide (**1a,b**; 5 mmol) in anhydrous benzene (100 mL). Afer 1 h acetylenic dipolarophiles (**5a,b**; 5 mmol) in benzene (20 mL) were added dropwise for 30 min (see Scheme II). Stirring was continued for 16-18 h. The excess of solvent was evaporated in vacuo, and the whole mass was then kept overnight at room temperature. Next day the residue containing triethylamine hydrobromide was filtered off and the filterate was concentrated to give the crude product. Separation of the crude product by column chromatography over neutral alumina using benzene as eluant gave a fraction which on recrystallization from ethanol gave the benzoindolizine derivatives (**7a-c**) in approximately 50-55% yield.

Preparation of Benzoindolizine Derivatives (9a-g) via Isoquinolinium Ylides. The reaction between phenacylisoquinolinium bromide (**2a-d**) (5 mmol), acetylenic dipolarophiles (**5a,b**), and triethylamine (0.7 cm^3) was conducted at room temperature for 18-20 h and the crude products were isolated

Table I. Structures and Physical Properties of Benzoindolizine Derivatives (Compounds 7a-c and 9a-g)[c]

compd	molecular formula	R	R′	R″	mp, °C	yield, %
7a	$C_{23}H_{17}NO_5$	C_6H_5	CO_2CH_3	CO_2CH_3	198-199[a]	50
7b	$C_{24}H_{19}NO_5$	4-$CH_3C_6H_4$	CO_2CH_3	CO_2CH_3	192-193	55
7c	$C_{23}H_{19}NO_3$	4-$CH_3C_6H_4$	H	$CO_2C_2H_5$	150-155	50
9a	$C_{23}H_{17}NO_5$	C_6H_5	CO_2CH_3	CO_2CH_3	150-158[b]	50
9b	$C_{22}H_{17}NO_3$	C_6H_5	H	$CO_2C_2H_5$	138-139	50
9c	$C_{23}H_{16}ClNO_5$	4-ClC_6H_4	CO_2CH_3	CO_2CH_3	176-178	55
9d	$C_{22}H_{16}ClNO_3$	4-ClC_6H_4	H	$CO_2C_2H_5$	173-175	60
9e	$C_{24}H_{19}NO_5$	4-$CH_3C_6H_4$	CO_2CH_3	CO_2CH_3	154-158	50
9f	$C_{23}H_{19}NO_3$	4-$CH_3C_6H_4$	H	$CO_2C_2H_5$	143-144	50
9g	$C_{24}H_{19}NO_6$	4-$OCH_3C_6H_4$	CO_2CH_3	CO_2CH_3	160-164	50

[a] Lit. (*8*) 194-196 °C. [b] Lit. (*8*) 155-156 °C. [c] Satisfactory elemental analyses were obtained for all compounds.

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Table II. Spectral Properties of Benzoindolizine Derivatives

product	spectral data	no. of H	assignment
7a	UV spectrum ($CHCl_3$) λ_{max} 260, 315, 335, 375 nm; log ϵ 3.92, 3.62, 3.57, 3.34		
	IR (KBr), cm^{-1}		
	2930		C–H
	1725		C=O, ester
	1690		C=O
	1625		C=C
7b	UV spectrum ($CHCl_3$) λ_{max} 270, 310, 330, 403, 460 nm; log ϵ 3.95, 379, 3.64, 3.49, 3.51		
	IR (KBr), cm^{-1}		
	2990		C–H
	1745		C=O, ester
	1675		C=O
	1620		C=C
7c	UV spectrum ($CHCl_3$) λ_{max} 260, 310, 340, 385 nm; log ϵ 3.93, 3.78, 353, 3.60		
	IR (KBr), cm^{-1}		
	2990		C–H
	1685		C=O, ester
	1620		C=O
	1600		C=C
	^1H NMR ($CDCl_3$) δ		
	8.27 d	1	C_{10}-H
	8.10–7.20 m	9	Ar-H
	2.47 s	3	methyl
	1.37 t	3	methyl
	4.37 q	2	methylene
9a	^1H NMR ($CDCl_3$) δ		
	9.56 d ($J_{5,6}$ = 8.33 Hz)	1	C_5-H
	9.66 m	1	C_{10}-H
	7.1 d ($J_{5,6}$ = 8.33 Hz)	1	C_6-H
	7.2–7.9 m	8	Ar-H
	3.95 s and 3.26 s	2 × 3 H	2 × methyl
9b	UV ($CHCl_3$) λ_{max} 270, 310, 360, 380 nm; log ϵ 3.85, 3.70, 3.54, 3.64		
	^1H NMR ($CDCl_3$) δ		
	9.5 d ($J_{5,6}$ = 8.3 Hz)	1	C_5-H
	9.68 m	1	C_{10}-H
	7.2–8.0 m	9	Ar-H
	7.1 d ($J_{5,6}$ = 8.3 Hz)	1	C_6-H
	4.4 q	2	CH_2
	1.36 t	3	methyl
9c	^1H NMR ($CDCl_3$) δ		
	8.9 d ($J_{5,6}$ = 8 Hz)	1	C_5-H
	9.06 m	1	C_{10}-H
	7.1 d ($J_{5,6}$ = 8 Hz)	1	C_6-H
	7.26–7.86 m	7	Ar-H
	3.96 s and 3.36 s	2 × 3	2 × methyl
9d	^1H NMR ($CDCl_3$) δ		
	9.5 d ($J_{5,6}$ = 8.3 Hz)	1	C_5-H
	9.74 m	1	C_{10}-H
	7.1 d ($J_{5,6}$ = 8.3 Hz)	1	C_6-H
	7.2–7.88 m	8	Ar-H
	4.32 q	2	methylene
	1.32 t	3	methyl
9e	IR (KBr), cm^{-1}		
	2930		C–H
	1725		C=O, ester
	1690		C=O
	1580		C=C
9f	^1H NMR ($CDCl_3$) δ		
	9.48 d ($J_{5,6}$ = 8.36 Hz)	1	C_5-H
	9.78 m	1	C_{10}-H
	7.24 d ($J_{5,6}$ = 8.36 Hz)	1	C_6-H
	7.4–7.98 m	8	Ar-H
	4.43 q	2	methylene
	1.37 t	3	methyl
	2.45 s	3	methyl
9g	UV ($CHCl_3$) λ_{max} 270, 300, 360, 376 nm; log ϵ 4.25, 4.00, 3.76, 3.82		
	^1H NMR ($CDCl_3$) δ		
	8.43 d ($J_{5,6}$ = 7.63 Hz)	1	C_5-H
	8.63 m	1	C_{10}-H
	6.83 d ($J_{5,6}$ = 7.63 Hz)	1	C_6-H
	6.89–9.03 m	7	Ar-H
	3.93 s	3	methoxy
	3.89 s and 3.35 s	2 × 3 H	2 × methyl

in the usual manner (see Scheme III). Chromatography over neutral alumina using benzene as eluant gave a fraction which on recrystallization from ethanol afforded benzoindolizine derivatives (9a–g) in 50–60% yield.

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Reactions with Heterocyclic Diazonium Salts. Synthesis of Several New Fused Azolotriazine Derivatives

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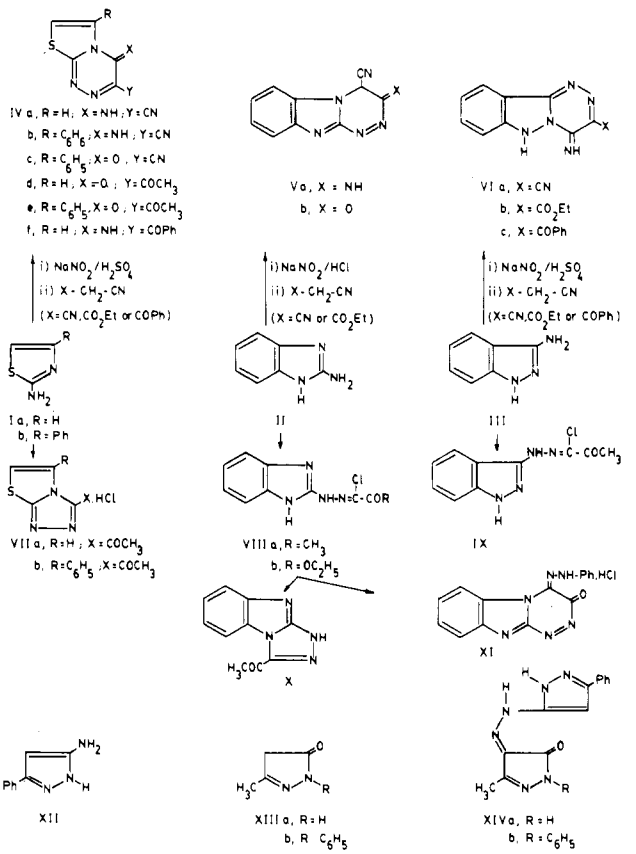
A variety of azolo-1,2,4-triazine derivatives were prepared via coupling diazotized aminoheterocyclic derivatives with activated nitriles. Coupling of diazotized amino heterocycles with α-chloroacetylacetone and/or ethyl α-chloroacetoacetate afforded fused 1,2,4-triazoles. The intermediately formed heterocyclic hydrazonyl halides could be isolated in some cases.

In continuation of our work aiming to explore the synthetic potentialities of heterocyclic diazonium salts (*1*–*3*), we report here our further results in this direction. Thus, the diazotized aminoheterocyclic derivatives Ia,b, II, and III coupled with activated nitriles to yield the azolotriazine derivatives IVa–f, Va,b, and VIa–c. Similarly diazotized Ia,b coupled with α-chloroacetylacetone to yield the thiazolo[3,2-*c*]-1,2,4-triazole derivatives VIIa,b. On the other hand, the hydrazonyl chlorides VIIIa,b were obtained on coupling diazotized II with α-chloroacetylacetone and with ethyl α-chloroacetoacetate. Also compound III coupled with α-chloroacetylacetone to yield the hydrazone IX. Compound VIIIa could be cyclized into the benzimidazo[1,2-*c*]-1,2,4-triazole derivative X. On the other hand, VIIIb cyclized into the benzimidazo[1,2-*c*]-*as*-triazine derivative XI by the action of phenylhydrazine.

Similar to previous work (*3*), diazotized 5-amino-3-phenylpyrazole (XII) coupled with the 2-pyrazolin-5-one derivatives XIIIa,b to yield the hydrazones XIVa,b. Compounds XIVa,b did not cyclize into pyrazolotriazines under conditions reported to effect cyclization of structurally related hydrazones.

The structures of the synthesized products were established on the basis of analytical and spectral data.



Experimental Section

All melting points are uncorrected. IR spectra were recorded (KBr) with a Beckman spectrophotometer. ^{1}H NMR spectra were obtained on an EM-390 90-MHz spectrophotometer using Me_4Si as internal indicator, and chemical shifts are expressed in ppm. Analytical data were obtained from the analytical data unit at Cairo University.

Reaction of Diazotized Ia,b, II, III, and XII with Active Hydrogen Compounds. A solution of 0.01 mol of diazotized Ia,b and III (prepared following the procedure described by

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