Synthesis of benzoindolizine derivatives by reaction of trimethyl phosphite, dialkyl acetylenedicarboxylates and isoquinolinium or quinolinium bromides

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The reactive 1:1 adduct produced by the addition of trimethyl phosphite to dialkyl acetylenedicarboxylates protonated by isoquinolinium or quinolinium bromides to afford isoquinolinium or quinolinium ylides and vinyl phosphonium bromides. 1,3-Dipolar cycloaddition reaction between isoquinolinium or quinolinium ylides and vinyl phosphonium bromides, followed by elimination of dimethyl phosphite and subsequent air-oxidation led to benzoindolizine derivatives in good yields.

Keywords: dialkyl acetylenedicarboxylates, trimethyl phosphite, 1,3-dipolar cycloaddition, benzoindolizine derivatives, quinolinium ylides

The indolizines are of considerable interest from the physical, chemical and biological points of view.[1,2] The presence of a carbamoyl group on the pyrrole ring of the indolizines should have interesting effects on their chemical and biological properties. One of the most important methods for the synthesis of indolizine and benzoindolizine derivatives is based on 1,3-dipolar cycloaddition reactions of *N*-heterocyclic ylides with electron-deficient alkynes or alkenes.[3-5] The *N*-heterocyclic ylides could be obtained by the dehydrohalogenation of the corresponding quaternary salts of *N*-heterocyclic compounds.[4,6]

The reaction of trimethyl phosphite and dimethyl acetylenedicarboxylate (DMAD) in the presence of alcohols reported to produce phosphite ylide derivatives which are stable at low temperatures, but are converted to phosphonate derivatives by warming or by treatment with water.[7] There are other recent reports on the reaction between phosphites and acetylenic esters in the presence of an acidic organic compound, all proceeding through a phosphite ylide intermediate.[8-14] In continuation of our previous work on the reaction between trivalent phosphorus nucleophiles and acetylenic esters in the presence of organic NH, OH, or CH-acids,[9-14] we report here the results of our study on the reaction between dialkyl acetylenedicarboxylates and trialkyl phosphites such as triethyl phosphite, tributyl phosphite or trimethyl phosphite in the presence of C–H acidic compounds isoquinolinium or quinolinium bromides.

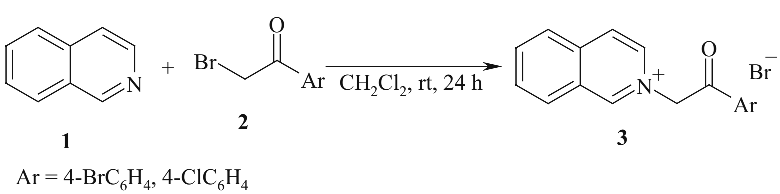
Results and discussion

Treatment of isoquinoline with 4-bromo or 4-chloro-phenacylbromide in dichloromethane after 24 h gave the corresponding isoquinolinium bromide derivatives in nearly quantitative yields (Scheme 1). Reaction of dimethyl acetylenedicarboxylate (DMAD, **4a**) with trimethyl phosphite in the presence of 2-[2-(4-bromophenyl)-2-oxoethyl)]isoquinolinium bromide (**3a**) after separation by column chromatography gave dimethyl 3-(4-bromobenzoyl) benzo[*g*]indolizine-1,2-dicarboxylate **5a** in 83% yield (Scheme 2). Similar products were obtained using diethyl acetylenedicarboxylate (DEAD) as activated acetylene or 2-[2-(4-chlorophenyl)-2-oxoethyl)]isoquinolinium bromide as the C–H acidic compound. Under the same conditions, the reaction between dimethyl acetylenedicarboxylate (DMAD, **4a**) with 2-[2-(4-bromophenyl)-2-oxoethyl)]isoquinolinium bromide (**3a**) was examined in the presence of triethyl phosphite or tributyl phosphite, instead of trimethyl phosphite, and the same product **5a** was obtained in similar 85 and 80% yields, respectively.

Products **5a–d** were all new compounds and their structures were deduced from their elemental analyses and spectral data. The ^{1}H NMR spectrum of compound **5a** displayed two sharp single signals at 3.33 and 3.94 ppm for methoxycarbonyl groups, along with characteristic signals at 7.13–8.85 ppm for the aromatic protons. The IR spectrum of compound **5a** exhibited strong absorption bonds at 1735, 1730 and 1623 cm^{-1} for two esters and one ketone carbonyl groups. The ^{13}C NMR spectrum of compound **5a** showed 21 signals in agreement with the proposed structure.

Similar reaction of activated acetylenes were examined with quinolinium ylides instead of isoquinolinium ylides in the presence of trimethyl phosphite. As shown in Scheme 3, 1-[2-(4-halophenyl)-2-oxoethyl)]quinolinium bromides can be easily prepared by treatment of quinoline with 4-bromo or 4-chloro-phenacylbromide in dichloromethane after 24 h in nearly quantitative yields. Reaction of dialkyl acetylenedicarboxylates **4** with trimethyl phosphite in the presence of 1-[2-(aryl)-2-oxoethyl)]quinolinium bromide **6** after separation by column chromatography afforded dialkyl 1-(4-aroyl)benzo[*e*]indolizine-2,3-dicarboxylates **7a–d** in 75–85% yields (Scheme 4).

Although we have not established the mechanism of the reaction between trimethyl phosphite and an acetylenic ester in the presence of quinolinium bromide **6** experimentally, a possible explanation is proposed in Scheme 5. The initial addition of phosphite on acetylene diester leads to a diionic intermediate that then protonated by quinolinium bromide **6** to produce vinyl phosphonium bromide **9** and quinolinium ylide **8**. The 1,3-dipolar cycloaddition reaction between intermediates



Scheme 1

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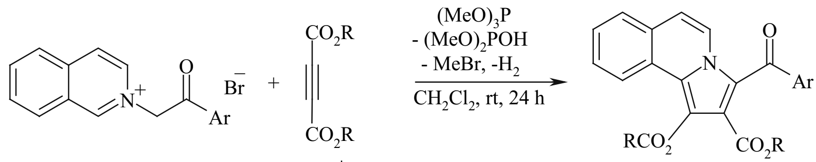


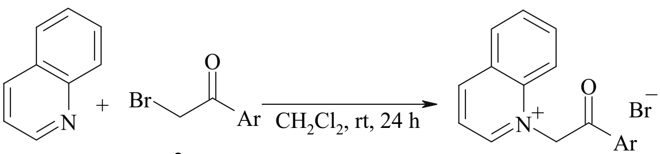
3	Ar
a	4-BrC_6H_4
b	4-ClC_6H_4

4	R
a	Me
b	Et

5	Ar	R	%Yield* of **5**
a	4-BrC_6H_4	Me	83
b	4-BrC_6H_4	Et	78
c	4-ClC_6H_4	Me	75
d	4-ClC_6H_4	Et	80

*Isolated yields

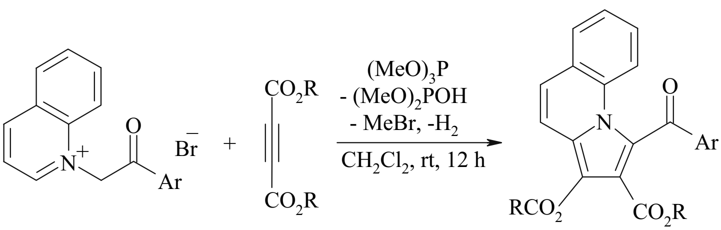
Scheme 2



2 **6**

Ar = 4-BrC_6H_4, 4-ClC_6H_4

Scheme 3



6 **4** **7**

7	Ar	R	%Yield* of **7**
a	4-BrC_6H_4	Me	80
b	4-ClC_6H_4	Me	85
c	4-ClC_6H_4	Et	75
d	4-ClC_6H_4	t-Bu	79

*Isolated yields

Scheme 4

8 and **9** afforded the tricyclic intermediate **10**. Elimination of dimethyl phosphite from intermediate **10** followed by the air-oxidation afforded the product **7**.

In summary, we report here that reaction between trialkyl phosphites, dialkyl acetylenedicarboxylates and isoquinolinium or quinolinium bromides afforded benzoindolizine derivatives in good yields. The presented method has the advantage of being performed under neutral conditions and requires no activation nor modification of the reagents.

Experimental

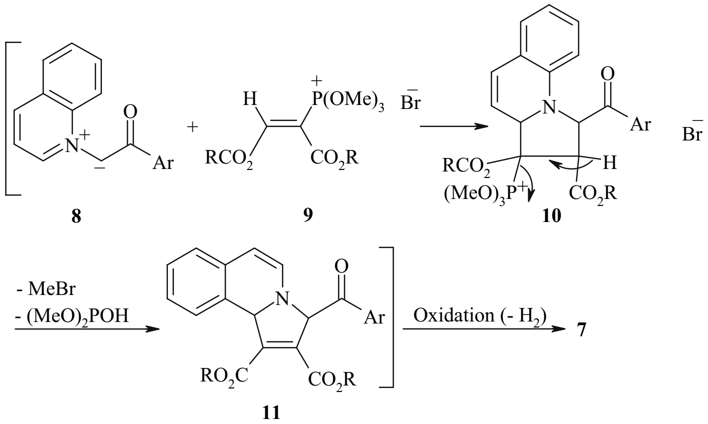
All melting points are uncorrected. Elemental analyses were performed using a Heraeus CHN–O–Rapid analyser. Mass spectra were recorded on a Finnigan-Mat 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^1H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at 500.1 and 125.8 MHz, respectively. ^1H and ^{13}C NMR spectra were obtained on solution in $CDCl_3$ using TMS as internal standard. Column chromatography was performed on Merck silica gel 60, 230–400 mesh. The chemicals used in this work purchased from Fluka (Buchs, Switzerland) and were used without further purification.

2-[2-(4-bromophenyl)-2-oxoethyl)]isoquinolinium bromide (**3a**): *Typical procedure for preparation of isoquinolinium or quinolinium bromides*

An equimolar mixture of isoquinoline and 4-bromophenacyl bromide in CH_2Cl_2 was stirred at room temperature for 24 h. The solvent was removed and the obtained powder was washed with diethyl ether and used for the next step.

Dimethyl3-(4-bromobenzoyl)benzo[g]indolizine-1,2-dicarboxylate (**5a**): *Typical procedure for preparation of benzoindolizines* **5a–d** *and* **7a-d**

To a magnetically stirred solution of DMAD (**4a**, 1 mmol) and 2-[2-(4-bromophenyl)-2-oxoethyl)]isoquinolinium bromide (**3a**, 1 mmol) in 10 ml CH_2Cl_2 was added a mixture of trimethyl phosphite (1.1 mmol) in 1 ml CH_2Cl_2 at room temperature. The reaction mixture was then stirred for 24 h. The solvent was removed under



Scheme 5

reduced pressure and the residue was purified by silica gel column chromatography using hexane–ethyl acetate as eluent. The solvent was removed under reduced pressure to afford the product as a yellow powder.

Yellow powder, m.p. 196–198 °C, IR(KBr) (ν_{max}, cm^{-1}): 1735, 1732, 1623 (C=O). Analyses: Calcd for $C_{23}H_{16}BrNO_5$: C, 59.24; H, 3.46; N, 3.00; Found: C, 59.40; H, 3.58; N, 3.19%. MS (*m/z*,%): 465 (M$^{\cdot+}$, 5). ^{1}H NMR (500 MH$_Z$, CDCl$_3$): δ 3.33 and 3.94 (6 H, 2 s, 2 OCH$_3$), 7.13–8.85 (10 H, aromatic). ^{13}C NMR (125.8 MH$_Z$, CDCl$_3$): δ 52.51 and 53.04 (2 O*C*H$_3$), 110.21, 116.48, 122.86, 123.97, 124.63, 126.13, 127.62, 127.71, 128.00, 128.81, 129.59, 130.01, 130.85, 132. 06, 132.99, 138.98 (aromatic), 164.96, 166.20 (2 C=O ester), 186.36 (C=O ketone).

Diethyl 3-(4-bromobenzoyl)benzo[g]indolizine-1,2-dicarboxylate (**5b**): Yellow powder, m.p. 118–120 °C, IR(KBr) (ν_{max}, cm^{-1}): 1732, 1726, 1626 (C=O). Analyses: Calcd for $C_{25}H_{20}BrNO_5$: C, 60.74; H, 4.08; N, 2.83; Found: C, 60.96; H, 4.21; N, 2.69%. MS (*m/z*,%): 493 (M$^{\cdot+}$, 7). ^{1}H NMR (500 MH$_Z$, CDCl$_3$): δ 0.82 and 1.18 (6 H, 2 t, $^3J_{HH}$ = 7 H$_Z$, 2 CH$_3$), 3.55 and 4.26 (4 H, 2 q, $^3J_{HH}$ = 7 H$_Z$, 2 OCH$_2$), 6.98–8.94 (10 H, aromatic). ^{13}C NMR (125.8 MH$_Z$, CDCl$_3$): δ 13.63 and 13.97 (2 CH$_3$), 61.57 and 62.74 (2 O*C*H$_2$), 110.24, 115.98, 122.38, 122.92, 123.59, 124.35, 125.74, 127.23, 127.74, 128.38, 129.12, 129.58, 130.65, 131. 67, 132.58, 138.55 (aromatic), 164.12, 165.58 (2 C=O ester), 186.17 (C=O ketone).

Dimethyl 3-(4-chlorobenzoyl)benzo[g]indolizine-1,2-dicarboxylate (**5c**): Yellow powder, m.p. 172–174 °C, IR(KBr) (ν_{max}, cm^{-1}): 1733, 1730, 1620 (C=O). Analyses: Calcd for $C_{23}H_{16}ClNO_5$: C, 65.49; H, 3.82; N, 3.32; Found: C, 65.28; H, 3.94; N, 3.42%. MS (*m/z*,%): 421 (M$^{\cdot+}$, 7). ^{1}H NMR (500 MH$_Z$, CDCl$_3$): δ 3.14 and 3.75 (6 H, 2 s, 2 OCH$_3$), 6.98–8.66 (10 H, aromatic). ^{13}C NMR (125.8 MH$_Z$, CDCl$_3$): δ 52.11 and 52.65 (2 O*C*H$_3$), 109.78, 116.09, 122.52, 123.56, 124.24, 125.72, 127.24, 128.44, 128.69, 128.81, 129.21, 129.60, 130.35, 130. 91, 132.56, 139.04 (aromatic), 164.98, 166.32 (2 C=O ester), 186.41 (C=O ketone).

Diethyl 3-(4-chlorobenzoyl)benzo[g]indolizine-1,2-dicarboxylate (**5d**): Yellow powder, m.p. 147–149 °C, IR(KBr) (ν_{max}, cm^{-1}): 1736, 1732, 1628 (C=O). Analyses: Calcd for $C_{25}H_{20}ClNO_5$: C, 66.74; H, 4.48; N, 3.11; Found: C, 66.90; H, 4.33; N, 3.27%. MS (*m/z*,%): 449 (M$^{\cdot+}$, 5). ^{1}H NMR (500 MH$_Z$, CDCl$_3$): δ 0.83 and 1.19 (6 H, 2 t, $^3J_{HH}$ = 7 H$_Z$, 2 CH$_3$), 3.56 and 4.24 (4 H, 2 q, $^3J_{HH}$ = 7 H$_Z$, 2 OCH$_2$), 6.98–8.68 (10 H, aromatic). ^{13}C NMR (125.8 MH$_Z$, CDCl$_3$): δ 13.63 and 13.98 (2 CH$_3$), 61.55 and 61.72 (2 O*C*H$_2$), 110.22, 115.94, 122.38, 123.57, 124.35, 125.72, 127.21, 128.35, 128.69, 128.81, 129.09, 129.56, 130. 56, 130.90, 132.39, 139.15 (aromatic), 164.32, 165.51 (2 C=O ester), 185.83 (C=O ketone).

Dimethyl 1-(4-bromobenzoyl)benzo[e]indolizine-2,3-dicarboxylate (**7a**): Yellow powder, m.p. 202–204 °C, IR(KBr) (ν_{max}, cm^{-1}): 1735, 1689, 1645 (C=O). Analyses: Calcd for $C_{23}H_{16}BrNO_5$: C, 59.24; H, 3.46; N, 3.00; Found: C, 59.19; H, 3.63; N, 3.19%. MS (*m/z*,%): 465 (M$^{\cdot+}$, 9). ^{1}H NMR (500 MH$_Z$, CDCl$_3$): δ 3.30 and 3.91 (6 H, 2 s, 2 OCH$_3$), 7.43–8.25 (10 H, aromatic). ^{13}C NMR (125.8 MH$_Z$, CDCl$_3$): δ 52.22 and 52.82 (2 O*C*H$_3$), 106.13, 118.32, 119.35, 123.46, 125.72, 126.25, 126.32, 128.61, 129.51, 129.61, 129.73, 131.69, 132.44, 132. 83, 136.87, 137.68 (aromatic), 163.96, 165.50 (2 C=O ester), 186.96 (C=O ketone).

Dimethyl 1-(4-chlorobenzoyl)benzo[e]indolizine-2,3-dicarboxylate (**7b**): Yellow powder, m.p. 158–160 °C, IR(KBr) (ν_{max}, cm^{-1}): 1734, 1690, 1644 (C=O). Analyses: Calcd for $C_{23}H_{16}ClNO_5$: C, 65.49; H, 3.82; N, 3.32; Found: C, 65.30; H, 3.97; N, 3.11%. MS (*m/z*,%): 421 (M$^{\cdot+}$, 10).^{1}H NMR (500 MH$_Z$, CDCl$_3$): δ 3.30 and 3.71 (6 H, 2 s, 2 OCH$_3$), 7.06-8.07 (10 H, aromatic). ^{13}C NMR (125.8 MH$_Z$, CDCl$_3$): δ 51.83 and 52.42 (2 O*C*H$_3$), 110.19, 117.92, 118.94, 123.18, 125.31, 125.85, 128.21, 128.81, 129.05, 129.12, 129.32, 130.90, 131.22, 132. 46, 136.02, 140.46 (aromatic), 163.17, 165.24 (2 C=O ester), 183.55 (C=O ketone).

Diethyl 1-(4-chlorobenzoyl)benzo[e]indolizine-2,3-dicarboxylate (**7c**): Yellow powder, m.p. 136–138 °C, IR(KBr) (ν_{max}, cm^{-1}): 1731, 1691, 1641 (C=O). Analyses: Calcd for $C_{25}H_{20}ClNO_5$: C, 66.74; H, 4.48; N, 3.11; Found: C, 66.39; H, 4.70; N, 3.07%. MS (*m/z*,%): 449 (M$^{\cdot+}$, 8). ^{1}H NMR (500 MH$_Z$, CDCl$_3$): δ 0.91 and 1.21 (6 H, 2 t, $^3J_{HH}$ = 7 H$_Z$, 2 CH$_3$), 3.71 and 4.17 (4 H, 2 q, $^3J_{HH}$ = 7 H$_Z$, 2 OCH$_2$), 7.07–8.09 (10 H, aromatic). ^{13}C NMR (125.8 MH$_Z$, CDCl$_3$): δ 13.12 and 13.75 (2 CH$_3$), 61.12 and 61.64 (2 O*C*H$_2$), 110.32, 117.74, 119.08, 123.58, 125.61, 126.05, 128.43, 128.73, 129.00, 129.25, 129.64, 130.90, 131.36, 132. 55, 136.12, 140.32 (aromatic), 163.86, 164.57 (2 C=O ester), 183.24 (C=O ketone).

Di(tert-butyl) 1-(4-chlorobenzoyl)benzo[e]indolizine-2,3-dicarboxylate (**7d**): Yellow powder, m.p. 171–173 °C, IR(KBr) (ν_{max}, cm^{-1}): 1735, 1696, 1647 (C=O). Analyses: Calcd for $C_{29}H_{28}ClNO_5$: C, 68.84; H, 5.58; N, 2.77; Found: C, 68.98; H, 5.70; N, 2.51%. MS (*m/z*,%): 505 (M$^{\cdot+}$, 6). ^{1}H NMR (500 MH$_Z$, CDCl$_3$): δ 1.04 (9 H, s, *t*-Bu), 1.44 (9 H, s, *t*-Bu), 7.07–8.00 (10 H, aromatic). ^{13}C NMR (125.8 MH$_Z$, CDCl$_3$): δ 27.53 and 28.45 (6 CH$_3$ of 2 *t*-Bu), 81.39 and 82.45 (2 C of 2 *t*-Bu), 107.92, 118.27, 118.33, 123.18, 125.26, 125.42,126.54, 127.16, 128.79, 129.22, 129.30, 131.54, 132. 42, 135.97, 136.18, 140.70 (aromatic), 162.74, 162.91 (2 C=O ester), 184.16 (C=O ketone).

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