J. Chem. Research (S), 2002, 587–588
J. Chem. Research (M), 2002, 1201–1214

Quinazoline, pyrazolo[1,5-*c*]quinazoline and spiro quinazoline dimers from the reaction of 2-aminoacetophenone hydrazones with triphosgene

H.Z. Alkhathlan*, M.A. Al-Saad, H.M. Al-Hazimi, K.A. Al-Farhan and A.A. Mousa

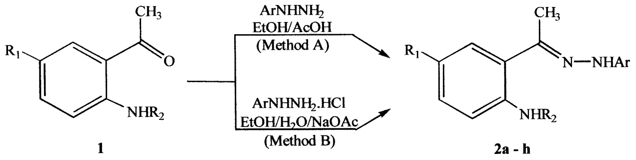
Department of Chemistry, College of Science, King Saud University, PO Box 2455,
Riyadh – 11451, Saudi Arabia

The reaction of hydrazones of 2-aminoacetophenone with triphosgene in dichloromethane or benzene in the presence of triethylamine gave quinazolines, pyrazolo[1,5-*c*]quinazoline and spiro quinazoline dimers. The latter compounds are being reported for the first time. In addition, a 4,4-disubstituted quinazoline derivative is prepared and its x-ray crystal structure is reported.

Keywords: hydrazones, o-aminoacetophenones, triphosgene, quinazolines, spiro compounds

While hydrazones of 2-aminobenzophenone have previously been used for the synthesis of benzotriazepines via their reaction with paraformaldehyde and phosgene[1,2], to the best of our knowledge there is no previous report on the reaction of hydrazones of 2-aminoacetophenone with phosgene or any other similar reagent.

In this paper we report the synthesis of quinazoline, pyrazolo[1,5-*c*]quinazoline and spiro quinazoline dimers from the reaction of hydrazones of 2-aminoacetophenone with triphosgene**.** Reaction of 2-aminoacetophenone with aromatic hydrazines in ethanol and acetic acid (Method A) or aromatic hydrazine hydrochlorides in ethanol, water and sodium acetate (Method B) afforded the hydrazones **2a–h** in very good yields (Scheme 1 and Table 1). Cyclisation of these hydrazones with triphosgene gave 4-methylenequinazoline, pyrazolo[1,5-*c*]quinazoline or the novel spiro ring system spiro[1*H*,4*H*-quinazoline-4,2′-[5*H*]pyrazolo[1,5-*c*]-1*H*-quinazoline-2,5-dione.



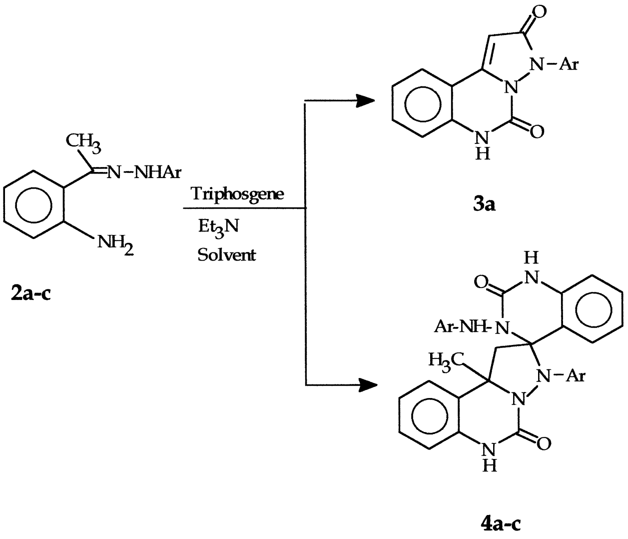
Scheme 1
Formation of arylhydrazones of 2-aminoacetophenones.

Table 1 Arylhydrazones formed according to Scheme 1

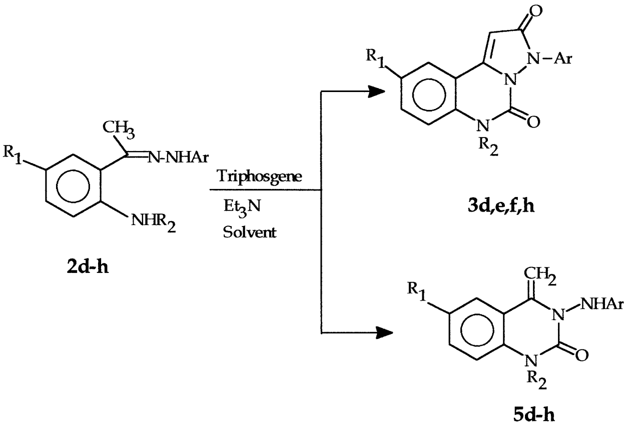
Compound	R_1	R_2	Ar	Method	Yield /%
2a	H	H	Ph	A	90
2a				B	75
2b	H	H	$4\text{-}NO_2C_6H_4$	A	75
2c	H	H	$2,4\text{-}(NO_2)_2C_6H_3$	A	85
2d	H	H	$4\text{-}BrC_6H_4$	B	68
2e	H	H	$4\text{-}ClC_6H_4$	B	72
2f	H	H	$4\text{-}CH_3C_6H_4$	B	63
2g	H	$COCH_3$	Ph	A	78
2h	Br	H	Ph	A	92

In case of hydrazones **2a–c**, products two and three were obtained from their reaction with one equivalent of triphosgene under basic conditions (Scheme 2).

While hydrazone **2a** gave a mixture of **3a** and **4a** with different ratios depending on which solvent is used (see later in the text), hydrazones **2b** and **2c** with a strong withdrawing group on the Ar substituent gave only the spiro compounds **4b** and **4c**, respectively. Treatment of hydrazones **2d–h** with triphosgene, in contrast, did not give any spiro compounds, but gave instead 4-methylenequinazolines **5d–h** along with **3d–h** (Scheme 3).



Scheme 2
Reaction of hydrazones **2a–c** with triphosgene



Scheme 3
Reaction of hydrazones **2d–h** with triphosgene

The pyrazolo[1,5-*c*]quinazolines **3a, d, e, f, h** showed in their IR spectra two absorption bands at 1713 and 1650 cm^{-1} for the

---

* To receive any correspondence. E-mail: khathlan@ksu.edu.sa

Table 2 Solvent effect on products ratios

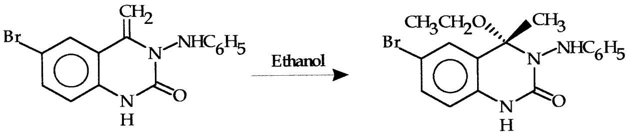
Solvent	Product ratios/%		
dichloromethane	**3a** (21)	**4a** (58)	–
"	–	**4b** (100)	–
"	–	**4c** (100)	–
"	**3d** (30)	–	**5d** (52)
"	**3e** (29)	–	**5e** (45)
"	**3f** (21)	–	**5f** (70)
"	–	–	**5g** (100)
"	**3h** (19)	–	**5h** (61)
benzene	**3a** (55)	**4a** (36)	–
"	–	**4b** (100)	–
"	–	**4c** (100)	–
"	**3d** (43)	–	**5d** (33)

two carbonyl groups at C2 and C5. The C1 proton appeared as a singlet at about δ 6.2 ppm in the ^{1}H-NMR and at about δ 90.0 ppm in the ^{13}C NMR. The spiro compounds **4a–c**, on the other hand, showed in their IR spectra one wide absorbance at about 1690 cm^{-1} for the two carbonyl groups. The ^{1}H NMR spectra of these compounds indicated the presence of a methyl group at δ 1.90 ppm and a methylene group at about δ 3.40–3.50 ppm. The IR spectra of the quinazoline derivatives **5d–h** showed absorption bands at 1700 cm^{-1} for the carbonyl group and 1600 cm^{-1} for the exocyclic double bond. The latter group appeared as broad doublet in the range between δ 4.7–5.9 ppm and at about δ 83.0 ppm in the ^{1}H and ^{13}C NMR, respectively.

As shown in Schemes 2 and 3, reaction of hydrazones **2a–h** with triphosgene gave mixtures of two products. The ratios of these products were found to be dependent on the type of solvent used (Table 2).

Finally, since we have previously observed that 4-methylene-1,3-benzoxazines upon treatment with ethanol gave 4,4-disubstituted compounds[13], we have now applied this reaction to compounds **5d–h**. Compound **5h**, chosen as a representative example, was treated with ethanol under refluxing conditions to give the 4,4-disubstituted quinazoline **6h** (Scheme 4). The structure of **6h** was confirmed using X-ray crystallography. Figure 1 shows the crystal structure of **6h**.

Techniques used: ^{1}H and ^{13}C NMR spectroscopy, MS, IR, X-ray crystallography.



5h **6h**

Scheme 4
Addition of ethanol to 4-methylenequinazolin, **5h**

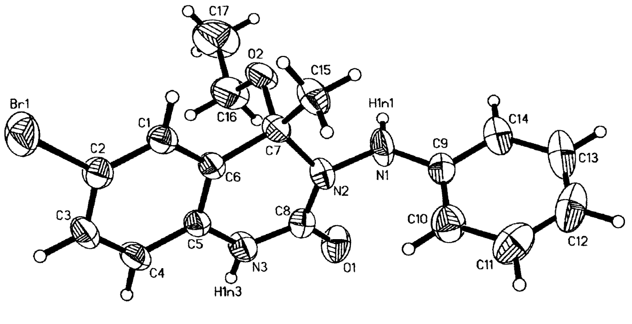


Fig. 1 X-ray crystal structure of **6h**.

Schemes: 4

Tables: 4

Table 3: Crystal data and structure refinement for **6h**

Table 4: Selected Bond Lengths (Å) and Angles (°) for **6h**

Figures: 1

Received 20 September 2002; accepted 29 October 2002
Paper 02/1558

References cited in this synopsis

1 T. Ishiwaka, M. Sano, K. Isagawa, and Y. Fushizaki, *Bull. Chem. Soc. Jap.*, 1970, **43**, 135.
2 H. Kohl, P.D. Desai, A.N. Dohadwalla and N.J. de Souza, *J. Pharm. Sci*, 1974, **63**, 838.
13 H.Z. Alkhathlan, *J. Heterocycl. Chem.* (in press).