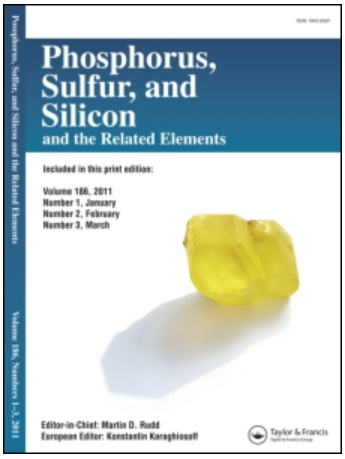


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# APPLICATION OF PHOSPHORUS, ARSENIC AND ANTIMONY REAGENTS IN THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS

Hamad Z. Alkhathlan[a]; Hamad A. Al-lohedan[a]
[a] Department of Chemistry, King Saud University, Riyadh, Saudi Arabia

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# APPLICATION OF PHOSPHORUS, ARSENIC AND ANTIMONY REAGENTS IN THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS

HAMAD Z. ALKHATHLAN and HAMAD A. AL-LOHEDAN
*Department of Chemistry, King Saud University, P.O. Box 2455, Riyadh-11451, Saudi Arabia*

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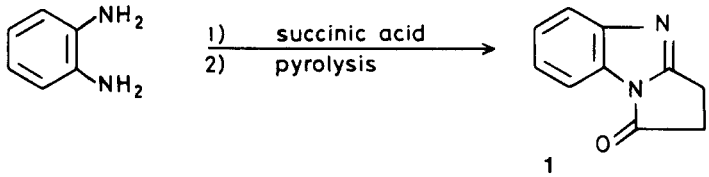
The ability of different reagents of the type $R_3XBr_2$, where R are various alkyl, alkoxide, phenyl, and phenoxide groups, and X is P, As and Sb, to promote an intramolecular cyclization of suitably substituted aromatic diamines has been investigated. The type of R group and X was found to have a great influence on the ability of these reagents to promote this type of cyclization. Best results were obtained when R=OMe and X=P.

*Key words:* Phosphorus; arsenic; antimony; dibromotriphenylphosphorane; diamines; heterocycles.



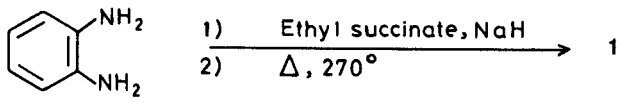
## INTRODUCTION

Synthesis of nitrogen heterocycles is an important field of organic research. A large number of methods using different reagents and strategies have been developed. Intramolecular cyclization of suitably substituted aromatic diamines is probably one of the best known methods. It was reported, as early as 1918, that when 1,2-phenylenediamine was treated with succinic acid followed by pyrolysis, 2,3-dihydro-1H-pyrrolo[1,2-a] benzimidazole-1-one **1** was obtained.[1] Others have reported similar reactions.[2]

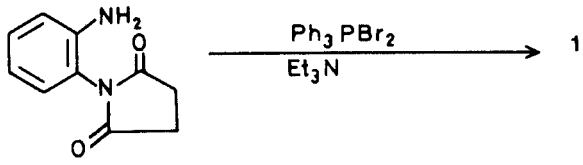



**1**

Intramolecular cyclization using 1,2-phenylenediamine and ethyl succinate in the presence of sodium hydride was also reported.[3]




Another method was later used to prepare several condensed heterocyclic compounds. It involves treatment of suitably substituted aromatic diamines with dibromotriphenylphosphorane in the presence of triethylamine,[4] i.e.

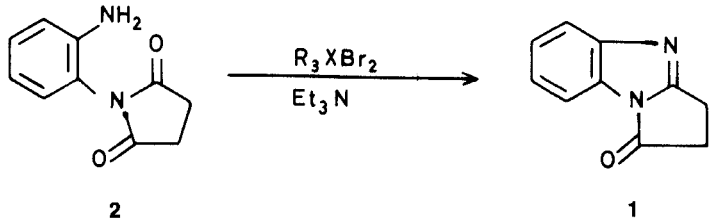



2

The aim of the present work is to investigate the effect of different reagents of the type $R_3XBr_2$, where R means various groups and X is P, As, Sb on the intramolecular cyclization of substituted aromatic diamines.

## RESULTS AND DISCUSSION

In order to examine the utility of the different reagents of the type $R_3XBr_2$ in their promotion of an intramolecular cyclization of substituted aromatic diamines, we have treated N-[2-aminophenyl]-2,5-pyrrolidinedione, **2**, with various reagents and compared the isolated yields of **1**.




**2** **1**

where, X = P and R = *n*-Bu, Ph, $PhCH_2$, MeO, PhO

X = As and R = Ph

X = Sb and R = Ph

## THE EFFECT OF SUBSTITUENT R IN $R_3XBr_2$

The effect of the type of R group in $R_3XBr_2$ on the utility of these reagents was investigated by the treatment of compound **2** with different $R_3XBr_2$ reagents. The results are summarized in Table I.

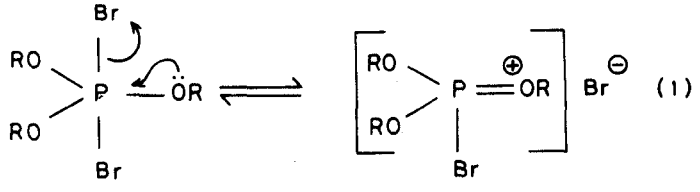
These results clearly show a large influence of the R group on the yield of reaction. Best results are obtained when R is a methoxy group while the lowest yield is obtained when R is a butyl group. A reasonable rationalization for the observed results is as follows. When R is a methoxy group, there will be a resonance between a lone pair of electrons from the oxygen and the pentavalent phosphorus producing an oxonium intermediate similar to that proposed for the reaction of ethers with dibromotriphenylphosphorane.[5]

Thus intermediate II will be more susceptible toward nucleophilic attack by the amino group in compound **1**. Of the five different groups that have been tested,

TABLE I
Isolated yields of **1** when X = P, R = various groups

| Reagent | % Yield of **1**[a] |
|---|---|
| $(n\text{-Bu})_3PBr_2$ | 35 |
| $(C_6H_5CH_2)_3PBr_2$ | 38 |
| $(C_6H_5)_3PBr_2$ | 58 |
| $(PhO)_3PBr_2$ | 65 |
| $(MeO)_3PBr_2$ | 80 |

[a] Yields of purified and recrystallized products.




I II



we would expect according to this proposal that the methoxy group would give the highest yield and that the phenoxy group would give the second best yield. In the latter case, the resonance shown in Equation (1) will be to a lesser extent because the oxygen lone pair of electrons is also in resonance with the aromatic ring. In addition to this, there is also a steric hindrance factor. A large phenyl group compared to a methyl group will certainly make the attack on the pentavalent phosphorus by the amino group more difficult and thus lower the yield. These two factors, the resonance and the steric hindrance effect, can then be used to explain the moderate yield obtained for the phenyl group and the relatively low yields for the benzyl and butyl groups.

Another advantage of the methoxy and phenoxy reagents, beside the high yields, is the ease of work-up of the reaction mixture. The resulting phosphate is water soluble and the heterocyclic compound can be obtained in a pure state by the addition of water to the reaction mixture and extracting with an organic solvent. On the other hand, when R is an alkyl or aryl group recrystallization was found to be necessary in order to purify the heterocyclic compound.

## THE EFFECT OF X IN $R_3XBr_2$

In order to investigate the effect of the central atom X, in $R_3XBr_2$, on the ability of these reagents to promote the intramolecular cyclization of substituted aromatic diamines we have used three different reagents. In these reagents the R group was always a phenyl group, while X is phosphorus, arsenic or antimony. The results are summarized in Table II.

In the first two cases where X is phosphorus or arsenic, good yields of **1** were obtained. However, when X is antimony none of **1** was formed. A TLC comparison

TABLE II

Isolated yields of **1** when R = Phenyl, X = P, As, Sb

| Reagent | % Yield of **1** |
|---|---|
| $Ph_3PBr_2$ | 58 |
| $Ph_3AsBr_2$ | 52 |
| $Ph_3SbBr_2$ | — |

between the reaction mixture and an authentic sample of **1** confirmed that compound **1** was actually not being formed in this case, where X is antimony. However, another TLC comparison between the same reaction mixture and an authentic sample of the starting material **2** showed that compound **2** did not react, under our conditions, with triphenylstibinedibromide. This might be related to the more metallic character of antimony compared with phosphorus and arsenic, which would give it a higher affinity for halogenes and make the displacement of the two halogen atoms by the amino group more difficult. This different behaviour for the antimony reagent from the phosphorus and arsenic analogous is not surprising. It has been shown before that triphenylstibinedibromide behaves in solution differently. It does not tend to ionize in solutions while the phosphorus and arsenic reagents ionize to a certain degree.[6]

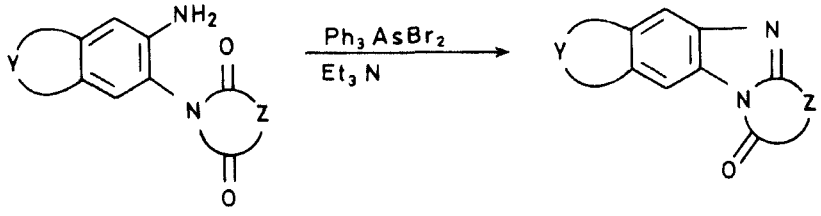


## THE EFFECT OF SUBSTRATE

Finally, the effect of the substrate (the starting substituted aromatic diamine) has been investigated. Different substrates were used in which the aromatic diamine part was changed, while in other cases a different acid anhydride was used.

These results are summarized in Table III.

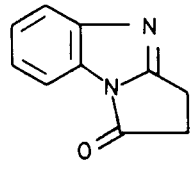
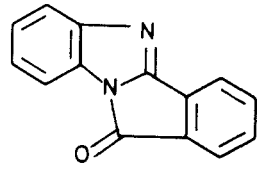
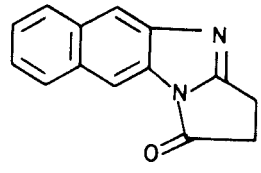
In conclusion, these reagents provide another alternative method for the promotion of intramolecular cyclization of substituted aromatic diamines. In addition to their availability, they require very mild conditions compared with some of the previous methods which require high temperatures or strong bases, such as sodium hydride. The present reagents require only reflux in dichloromethane.




**2, 3 a, b** **1, 4 a, b**

TABLE III

Effect of substrate on the cyclization

| Aromatic Diamine | Acid anhydride | Substrate | Heterocyclic product | Yield (%) |
|---|---|---|---|---|
| 1,2-Phenylenediamine | Succinic anhydride | **2** |  **1** | 52 |
| 1,2-Phenylenediamine | Phthalic anhydride | **3a** |  **4a** | 65 |
| 2,3-Diaminonaphthalene | Succinic anhydride | **3b** |  **4b** | 30 |



## EXPERIMENTAL

All melting points are uncorrected. NMR spectra were obtained on a Jeol FX100 (100 MHz) instrument with TMS as an internal standard in the indicated solvents.

*N-[2-Aminophenyl]-2,5-pyrrolidinedione*, **2**. This compound was obtained by refluxing 1,2-phenylenediamine with succinic anhydride in THF, in a procedure similar to that reported in Reference 4. 50% yield, mp 229–232°C (mp 235–237°C),[4] (230–232°C)[7a] (236–238°C)[7b] (244–245°C).[7c]

*N-(2-Aminophenyl)phthalimide*, **3a**. This compound was prepared analogously from 1,2-phenylenediamine and phthalic anhydride. 45% yield, mp 276–278°C. $^1$H NMR (DMSO): δ 7.7 (m, 2H), 7.5 (m, 4H); 7.2 (m, 2H). The peak due to the amino group was partially obscured by a peak at δ 2.6 due to a non-deuterated impurity of the deuteriodimethylsulfoxide.

*N-[2-(3-Aminonaphthyl)]-2,5-pyrrolidinedione* **3b**. This compound was prepared from 2,3-diaminonaphthalene and succinic anhydride. 48% yield, mp 200–202°C (202–204°C.)[4]

*Reaction of $R_3XBr_2$ with* **2**; *General Procedure*. One equivalent of $R_3XBr_2$ (prepared by a dropwise addition of one equivalent of $Br_2$ to a dichloromethane solution of $R_3X$) was added to a suspension of **2** in dichloromethane. Two equivalents of triethylamine were added dropwise and the reaction mixture

was then refluxed for about 10 hours. If unreacted starting material **2** was still present, it was filtered off and the filtrate was extracted with water. The organic fractions were collected, dried over anhydrous magnesium sulfate and then evaporated to dryness. When R is an aryl or alkyl, the resulting solid was recrystallized from ethanol. However when R is an alkoxy or phenoxy group, the product is pure enough and there is no need for recrystallization.

*2,3-Dihydro-1H-pyrrolo[1,2-a]benzimidazole-1-one,* **2**. This compound was prepared according to the general procedure mentioned above. Yields of **2** from the different reagents are shown in Table I, mp 172–173°C (175–176°C)[4] (171–172°C)[2a,b] (170°C).[1,3] $^1$H NMR ($CDCl_3$): δ 3.25 (m, 4H); 7.2 (m, 2H), 7.6 (m, 1H); 7.9 (m, 1H).

*1H-Isoindolo[2,1-a]benzimidazole-1-one,* **4a**. This compound was prepared analogously from **3a**, 65% yield, mp 209–211°C. $^1$H NMR ($CDCl_3$): δ 7.2 (m, 2H) 7.6 (m, 6H). $^{13}$C NMR ($CDCl_3$): δ 113, 120, 121, 123, 125, 126, 127, 130, 132, 135, 144, 148, 156, 161.

*2,3-Dihydro-1H-naphtho[2,3-d]pyrrolo[1,2-a]imidazole-1-one,* **4b**. This compound was prepared analogously from **3b**, 30% yield, mp 258–262°C (262–264°C).[4] $^1$H NMR ($CDCl_3$): δ 3.4 (m, 4H), 7.5 (m, 2H), 7.8 (m, 2H), 8.0 (S, 1H), 8.2 (S, 1H).

## ACKNOWLEDGEMENT

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