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Synthesis of 1,6-Diaryl-5,7-dioxo(dithio)imidazo[1,2-a][1,3,5]triazines. A Novel Pathway for Imidazo[1,2-a][1,3,5]triazine Systems Obtained via 1-(Imidazolin-2-yl)urea and Thiourea Derivatives

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Abstract

Novel 1,6-diaryl-5,7(1*H*)dioxo(dithio)-2,3-dihydroimidazo[1,2-a][1, 3, 5]triazines **8**, and **9** were synthesized by cyclization of the respective 1-(imidazolin-2-yl)ureas **4** or thioureas **6** with phosgene or thiophosgene in the presence of bases. 1-Aryl-2-aminoimidazolines **1** reacting with arylisocyanates **2** or arylisothiocyanates **3** form a mixture of isomeric imidazolin-2-yl **4** and **6** and imidazolin-3-yl **5** and **7** urea or thiourea derivatives. Isomers **4** and **6** can be easily separated and used for the cyclization reaction. The structures of the main intermediates and the final target compounds were confirmed by ^{1}H-NMR spectral analysis. Discussion of the possible course of the reactions is also presented.

Keywords: 1,6-diaryl-5,7(1*H*)dioxo(dithio)-2,3-dihydroimidazo[1,2-a][1,3,5]triazines, 1-(1-arylimidazolin-2-yl)-3-arylurea(thiourea), 1-aryl-2-imino-3-arylaminocarbonylimidazolidines, cyclization reactions with phosgene (thiophosgene).

Introduction

In recent years interest in the imidazo[1,2-a][1,3,5]triazine heterocyclic system has grown rapidly. This is mainly due to the strong antiviral activity some derivatives of this system exhibit [1-3]. The system has a structure isosteric to a purine ring system and its derivatives can be substrates of the Central and Peripheral Nervous Systems as well. So far, most synthetic methods applied to the formation of this system have started from the 1,3,5-triazine moiety [4, 5]. These methods are especially useful for introducing mixed (e.g. oxo and imino/amino) functions into the six membered part of the imidazo[1,2-a][1,3,5]triazine system. However, at the same time, they are much less useful for introducing different π-rich substituents (such as aromatic rings) into it. In this paper I will report the results of research concerning the reactions of 1-aryl-2-aminoimidazolines with arylisocyanates and their thio analogs, and cyclization of products obtained with phosgene or thiophosgene leading to 1,6-diaryl substituted imidazo[1,2-a][1,3,5]triazines.

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Results and Discussion

1-Aryl-2-aminoimidazolines **1,** as we have presented in previous papers, exist predominantly in the 2-imino tautomeric form [6]. Despite the double bond location in this type of molecule, the cyclic guanidine moiety easily undergoes 2+4 cyclocondensation reactions but usually furnishes a mixture of substitution isomers [6, 7], in contrast to 1-alkyl-5-aryl-2-amino-imidazolines **10** which exist predominantly in the 2-amino form and result only in one main product. On the other hand, a simple acylation reaction of **1** also leads to a mixture of isomers. In that case 1-aryl-2-aminoimidazolines reacted with arylisocyanates **2** or isothiocyanates **3** and formation of a mixture of isomers is observed [8]. ^{1}H-NMR spectra of the crude reaction product revealed two broad signals between 8.60-11.30 ppm which can be assigned to differently located hydrogens on *egso* N-2 or *endo* N-3 nitrogen atoms. Both signals are separated by ca. 2.80 ppm. The higher value (over 11.00 ppm) is probably that of 2-imino group, espe-

Table 1. *Physicochemical properties of 1-aryl-3-(1-aryl-imidazolin-2-yl)ureas **4** and thioureas **6**.*

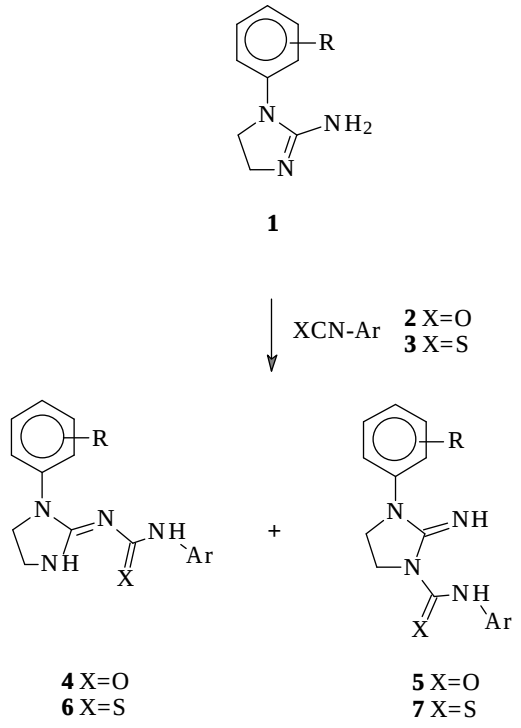
No	R	Ar	M.p.[^{0}C]	Yield[%]	Formula	^{1}H NMR spectra data($CDCl_3$, δ, ppm,TMS)
4a.	H	C_6H_5	158-9	84.2	$C_{16}H_{16}N_4O$	1.68 (s,2/3H, N-1); 2.36 (s, 1/3H, OH enol); 3.73 and 3.95 (2 x dd, 4H, C-4 and C-5); 7.14-7.57 (m,10H, aromatic H); 8.67 (bs, 1H, NH)
b.	H	3-ClC_6H_4	137-8	79.5	$C_{16}H_{15}ClN_4O$	
c.	H	4-ClC_6H_4	158-9	72.2	$C_{16}H_{15}ClN_4O$	1.68 (s, 2/3H, N-1); 2.36 (s, 1/3H, OH enol); 3.74 and 3.91 (2 x dd, 4H, C-4 and C-5), 7.14-7.58 (m, 9H, aromatic H); 8.67 (bs, 1H, NH)
d.	H	3,4-$Cl_2C_6H_3$	160-2	83.1	$C_{16}H_{14}Cl_2N_4O$	
e.	H	1-naphthyl	160-2	79.6	$C_{20}H_{18}N_4O$	
f.	4-CH_3	C_6H_5	178-80	57.7	$C_{17}H_{18}N_4O$	1.68 (s, 2/3H, N-1); 2.26 (s, 3H, CH_3); 2.35 (s, 1/3H, OH enol); 3.78 and 3.95 (2 x dd, 4H, C-4 and C-5); 7.14-7.58 (m, 9H, aromatic H); 8.67 (bs, 1H, NH)
g.	4-CH_3	3-ClC_6H_4	142-3	42.7	$C_{17}H_{17}ClN_4O$	
h.	4-CH_3	4-ClC_6H_4	158-9	57.8	$C_{17}H_{17}ClN_4O$	1.71 (s, 2/3H, N-1); 2.34 (s, 3H, CH_3); 2.38 (s, 1/3H, OH enol); 3.76 and 3.91 (2 x dd, 4H, C-4 and C-5); 7.19-7.42 (m, 8H, aromatic H); 8.61 (bs, 1H, NH)
i.	4-CH_3	3,4-$Cl_2C_6H_3$	167-9	82.6	$C_{17}H_{16}Cl_2N_4O$	
j.	4-CH_3	1-naphthyl	163-4	78.5	$C_{21}H_{20}N_4O$	
k.	4-Cl	C_6H_5	159-61	82.6	$C_{16}H_{15}ClN_4O$	
l.	4-Cl	3-ClC_6H_4	129-30	77.3	$C_{16}H_{14}Cl_2N_4O$	
m.	4-Cl	4-ClC_6H_4	174-5	74.5	$C_{16}H_{14}Cl_2N_4O$	
n.	4-Cl	3,4-$Cl_2C_6H_3$	187- 9	83.4	$C_{16}H_{13}Cl_3N_4O$	
o.	4-Cl	1-naphthyl	174-5	90.5	$C_{20}H_{17}ClN_4O$	
6a.	H	C_6H_5	163-6	61.0	$C_{16}H_{16}N_4S$	
b.	H	4-ClC_6H_4	187-90	70.0	$C_{16}H_{15}ClN_4S$	
c.	4-CH_3	C_6H_5	168-71	77.0	$C_{17}H_{18}N_4S$	1.62 (s, 1/2H, N-1); 2.36 (s, 3H, CH_3); 3.93 (m, 4H, C-4 and C-5); 6.95-7.26 (m, 9H, aromatic H); 7.99 (bs, 1H, NH); 10.38 (bs, 1/2H, SH thioenol)
d.	4-CH_3	3-ClC_6H_4	175-8	50.0	$C_{17}H_{17}ClN_4S$	
e.	4-CH_3	4-ClC_6H_4	198-200	58.0	$C_{17}H_{17}ClN_4S$	
f.	4-CH_3	4-$CH_3C_6H_4$	185-7	56.0	$C_{18}H_{20}N_4S$	
g.	4-Cl	C_6H_5	186-8	69.5	$C_{16}H_{15}ClN_4S$	
h.	4-Cl	4-ClC_6H_4	217-9	68.5	$C_{16}H_{14}Cl_2N_4S$	

Table 2. *Physicochemical properties of 1-aryl-2-imino-3-(arylaminocarbonyl)imidazolidine* ***4'***.

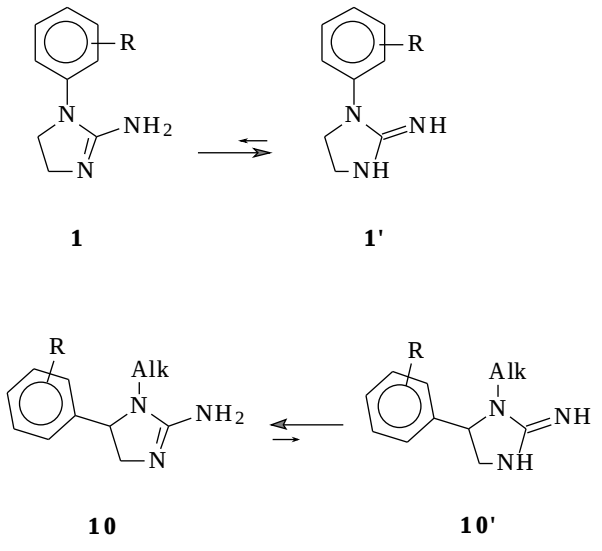
No	R	Ar	M.p.[^{0}C]	Yield[%]	Formula	^{1}H-NMR spectra data ($CDCl_3$, δ, ppm, TMS)
4'c.	H	4-ClC_6H_4	184-6	21.2	$C_{16}H_{15}ClN_4O$	1.91 (bs, 1/2H, N-1); 3.82 and 4.05 (2 x dd, 4H, C-4 and C-5); 6.00 (bs, 1/2H, OH enol); 7.10-7.52 (m, 9H,aromatic H); 12.45 (bs, 1H, NH)
f.	4-CH_3	C_6H_5	195-7	14.3	$C_{17}H_{18}N_4O$	1.69 (s, 2/3H, N-1); 2.34 (s, 3H, CH_3); 2.42 (s, 1/3H, OH enol); 3.76 and 3.88 (2 x dd, 4H, C-4 and C-5); 7.18-7.39 (m, 9H, aromatic H); 11.12 (bs, 1H, NH)
h.	4-CH_3	4-ClC_6H_4	183-5	13.6	$C_{17}H_{17}ClN_4O$	1.62 (s, 2/3H, N-1); 2.26 (s, 3H, CH_3); 2.31 (s, 1/3H, OH enol); 4.00 and 4.15 (2 x dd, 4H, C-4 and C-5); 7.01-7.40 (m, 8H, aromatic H); 11.26 (s, 1H, NH)

cially that carbonyl group conected with N-3 shows deshielding effect on C-4 and C-5 hydrogens downshifting their signals by 0.25 ppm in comparison to unsubstituted 2-aminoimidazolines. A similar downshift was reported previously for cyclic imidazo[1,2-a]pyrimidine-5-ones [6]. (Schemes 1 and 2, Tables 1 and 2)

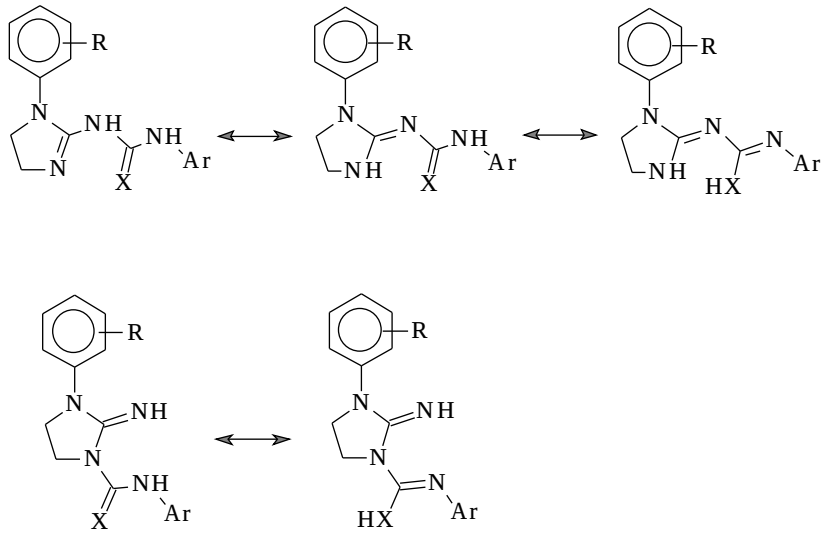
^{1}H NMR spectra also revealed the presence of tautomeric equilibrium between urea and isourea forms (Scheme 3, Tables 1 and 2). The presence of the enol form suggests that the group can be a nucleophilic center in the reaction with different alkyl or acyl chlorides, especially in the presence of bases. The reactions of **4** and **6** with phosgene or thiophosgene held under alkaline conditions led to cyclization of the six-membered ring. It has been found that cyclization approaches using only triethylamine or sodium hydride were not completely successful. In the first case, the reaction did not occur at all, while in the second one the product underwent decomposition and rearrangement during filtration (probably after contact with the air humidity). When a mixed alkaline medium - firstly containing sodium hydride and secondly containing triethylamine were used imidazo[1, 2-a][1,3,5]triazines were obtained in satisfactory yields. As illustrated in Scheme 4, the desired fusion can be achieved with imidazo[1,2-c][1,3,5]oxadiazines **11** as intermediates. ^{1}H-NMR spec-



Scheme 1



Scheme 2



Scheme 3

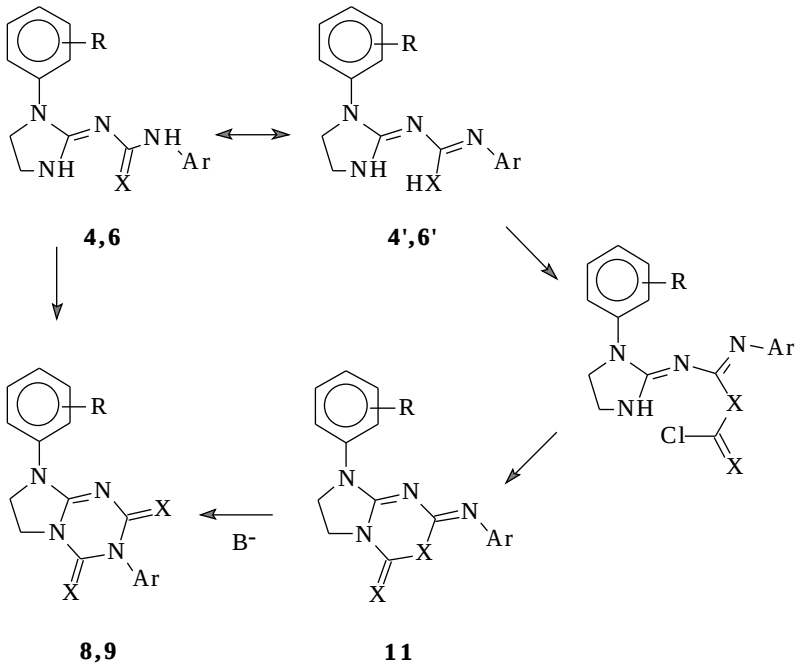
tra of the title compounds revealed two significant features of that structure. The first was the downshift of the C-4 and C-5 hydrogen signals, which suggests cyclic products, and the second was the widely separated signals of the hydrogens of the C-6 aromatic ring.

The structural model of structure **8** [9] (Fig. 1) shows, that by the specific location of the aromatic ring between two carbonyl groups, the C-6 aromatic hydrogens are strongly but unequally deshielded by them. It results in a spreading of their signals in a range near 1.00 ppm. This should not occur for structure **11** in which the double bond is coplanar with the aromatic ring .

Experimental Section

Melting points were measured using Boethius apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian Gemini 200 BB 200 MHz instrument. Elemental analysis was done on a Perkin-Elmer instrument and was in the satisfactory range of C-0.39%, H-0.47%, N-0.42%. Elemental analysis for Cl and S was carried out by the combustion and mercury perchlorate titration method and was in a satisfactory range of 0.5%.

All the procedures mentioned are general methods. The chemicals used in the reactions were from Merck



Scheme 3

(isocyanates and isothiocyanates) or Fluka (phosgene or thiophosgene).

1-(1-Phenylimidazolin-2-yl)-3-phenylurea.

To a solution of 11.9 g (0.1 mol) of phenylisocyanate in dry methylene chloride, a solution of 16.1 g (0.1 mol) 1-phenyl-2-aminoimidazoline in methylene chloride was added and the mixture was stirred for 6 hours at ambient temperature under a nitrogen atmosphere. The mixture was left overnight, the solvent was removed and the residue was dissolved in a mixture of isopropanol/acetone (10:1) and refrigerated for 2 hours. White crystals were collected and crystallized from isopropanol a few times until colourless needles were precipitated.

Column chromatography on 350 g of Merck Silica-gel F_{254} of 150 mg of the crude reaction product with 1500 ml of benzene/ethyl ether (1:1) and then with 600 ml of methylene chloride yielded 115 mg of the above-named product.

1-(4-Methylphenyl)-2-imino-3-(4-chlorophenylaminocarbonyl)imidazolin

Following the above procedure using 4-chlorophenylisocyanate and 1-(4-methylphenyl)-2-aminoimidazoline, a mixture of two isomeric forms was obtained. After solvent removal, a mixture of isopropanol/acetone (5:1) was added and the solution was refrigerated for 6 hours. White crystals were treated several times with a methanol/DMF mixture until colourless plates were precipitating. Treatment of the crude reaction product with isopropanol/acetone yielded colourless needles of 1-(4-chlorophenyl)-3-[1-(4-methylphenyl)imidazolin-2-yl]urea.

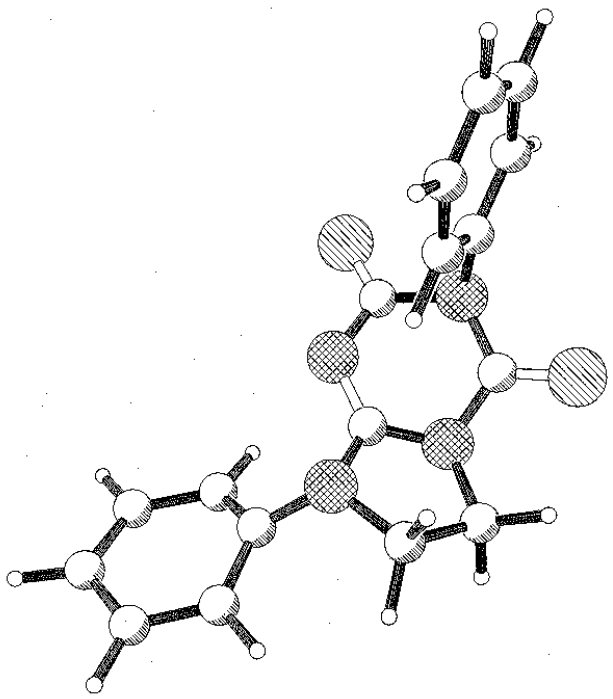


Figure 1. *Structural model of the triazine* ***8****.*

1-Phenyl-6-(4-chlorophenyl)-5,6(1H)dioxo-2,3-dihydroimidazo[1,2-a][1,3,5]triazine

A mixture of 15.7 g (0.05 mol) of 1-(1-phenylimidazolin-2-yl)-3-(4-chlorophenyl)urea and 2.5 g (0.05 mol) of 50% NaH oil suspension in dry toluene was stirred at ambient temperature in a nitrogen atmosphere for 2 hours. The mixture was cooled to -10 °C and 25 g (0.05 mol) 20% phosgene in toluene solution was added drop by drop. The mix-

Table 3. *Physicochemical properties of 1,6-diaryl-5,7(1H) dioxo* ***8*** *and dithio* ***9*** *-2,3-dihydroimidazo[1,2-a]-[1,3,5] triazines.*

No	R	Ar	M.p.[°C]	Yield[%]	Formula	^{1}H-NMR spectra data ($CDCl_3$, δ, ppm, TMS)
8b.	H	3-ClC_6H_4	293-4	31.4	$C_{17}H_{13}ClN_4O_2$	
8c.	H	4-ClC_6H_4	260-2	64.6	$C_{17}H_{13}ClN_4O_2$	3.67 and 4.07 (2 x dd, 4H, C-2 and C-3); 7.02-7.64 (m, 4H,N-6 aromatic H); 7.14-7.7.36 (m, 5H, N-1 aro matic H)
8e.	H	1-naphthyl	280-1	37.9	$C_{21}H_{16}N_4O_2$	
8h.	4-CH_3	4-ClC_6H_4	267-9	34.5	$C_{18}H_{15}ClN_4O_2$	2.26 (s, 3H, CH_3); 3.75 and 3.92 (2 x dd, 4H, C-2 and C-3); 6.98-7.68 (m, 4H, N-6 aromatic H); 7.18-7.38 (m, 4H, N-1 aromatic H)
8k.	4-Cl	C_6H_5	253-5	29.4	$C_{17}H_{13}ClN_4O_2$	
9b.	H	4-ClC_6H_4	213-5	49.5	$C_{17}H_{13}ClN_4S_2$	3.94 (m, 4H, C-2 and C-3); 6.96-7.44 (m, 4H, N-6 aro matic H); 7.15-7.39 (m, 5H, N-1 aromatic H)

ture was stirred for 4 hours until the contents of the flask became thick, the temperature was then allowed to rise to the room temperature and a solution of 5.0 g of triethylamine in dry toluene was added. The mixture was stirred for another 2 hours and then refluxed for 3 hours and allowed to cool. The precipitate was collected and recrystallized from a mixture of methanol and DMF.

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8. Sequence of reagents addition is very important due to formation of 1,3-diarylureas when solution of arylisocyanate is added to solution of 1-aryl-2-aminoimidazolines.
9. Model of hypothetical structure was drown in Department of Crystallography University of Marie Curie-Sklodowska, Lublin.