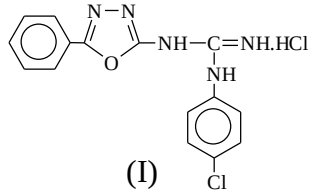
Synthesis of some substituted diazoles and triazoles from primary amines

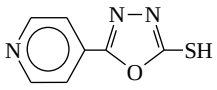
Khalid M. Daoud & Shaima S. Ismaeel
Chemistry Department, College of Education, University of Mosul

Abstract
In this paper the synthesis of substituted 1,3,4-oxadiazoles, thiadiazole and 1,2,4-triazoles. Cyclohexyl and hexylamine were treated with methyl chlorofomate to give the corresponding methyl N-alkyl carbamate (1,2), which converted to 4-alkyl semicarbazide (3,4) by their reaction with hydrazine hydrate in ethanol. Compounds (3,4) were treated with ammonium thiocyanate / hydrochloric acid to give substituted thiosemicarbazides (5,6). The thiosemicarbazides were treated with concentrated sulfuric acid or sodium hydroxide solution to give 5-amino-2-methyl amino-1,3,4-thiadiazole (9,10) and 5-methyl amino-1,2,4-triazoles-3-thiol (11,12) respectively. The substituted thiosemicarbazide was converted to 3,4-diamino-5-methyl amino-1,2,4-triazole (16) by its reaction with hydrazine hydrate. Compounds (3,4) were treated with carbon disulfide in potassium hydroxide to give substituted oxadiazoles (7,8). The reaction of 1,3,4-oxadiazoles with hydrazine hydrate gave substituted 1,2,4-triazoles (13,14), while compound (3) gave 4-amino-3,5-dicyclohexyl amino-1,2,4-triazole (15) upon heating at 90-120 °C.
The structure of the synthesized compounds were confirmed by spectral and physical methods.

Introduction
The five membered ring heterocyclic compounds with three heteroatoms as oxadiazoles, thiadiazoles and triazoles are known to possess various biological activities. Compound (I) shows anti-inflammatory activity[1], and compound (II) has strong activity against tuberculosis[2].

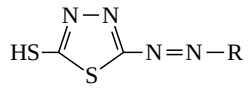


(I)

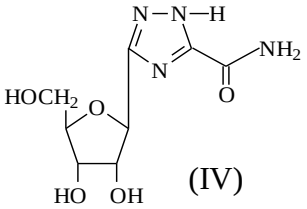


(II)

1,3,4-Thiadiazoles shows anticancer activity[3], substituted 1,3,4-thiadiazole used as fiber pigment compound (III)[4]. Whereas 1,2,4-triazole derivatives show antifungal activity[5] and anticancer agent as compound (IV)[6].

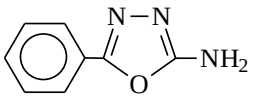


(III)



(IV)

The synthesis of 1,3,4-oxadiazole derivatives were obtained from acid hydrazide by its reaction with carbon disulfide in pyridine[7], or in alcoholic potassium hydroxide[8-10]. Thiosemicarbazide was used to synthesized substituted 1,3,4-oxadiazole by its reaction with lead oxide[11] or with acetic anhydride[12]. Dehydrating agents were applied on the synthesis of 1,4-diketone[13] as in the synthesis of compound (V).



(5)

1,3,4-Thiadiazole derivatives were synthesized from substituted thiosemicarbazides by their reaction with concentrated sulfuric acid[14,15], phosphoric acid[16] or hydrogen peroxide[17]. 1,2,4-Triazoles synthesized by the reaction of substituted thiosemicarbazide with sodium hydroxide[18,19].

Experimental
All chemicals were purchased from Flucka and BDH Chemical Ltd. The melting points were measured on an Electrothermal 9300 Engineering LTD and were uncorrected. IR spectra were recorded on Infrared Spectrophotometer Model Tensor 27, Bruker Co., Germany, using KBr discs. UV spectra were recorded on Shimadzu Double-Beam Spectrophotometer UV-210 A using ethanol as a solvent

Methyl-N-alkyl carbamate (1,2)[20]
A mixture of amine (0.075 mole), methyl chloroformate (11 g, 0.075 mole), and sodium bicarbonate (10 g) in absolute ethanol (40 ml) was refluxed for (3 h), the solvent then evaporated, and crushed-ice was added with stirring, the resultant mixture was extracted with ether (2 × 30 ml), the ether layer dried with magnesium sulfate, and evaporated under reduced pressure to give the products compound (1) was recrystallized from ethanol and (2) as pale yellow oil, Tables (1,2).

4-Alkyl semicarbazide (3,4)[21]
The ester (1 or 2) (0.07 mole) was added to hydrazine hydrate (1.8 ml, 0.035 mole) in absolute ethanol (30 ml). The mixture was refluxed for (3 h), the solvent was evaporated under reduced pressure to give compound (3) which was purified by recrystallization from ethanol, and compound (4) as oil, Tables (1,2).

1-Alkyl aminocarbonyl thiosemicarbazide (5,6)[22]
A mixture of 4-alkyl semicarbazide (3 or 4) (0.013 mole), ammonium thiocyanate (3 g, 0.037 mole) and hydrochloric acid (6 ml) in absolute ethanol (40 ml) was refluxed for (22 h), the solvent was evaporated under reduced pressure, the residue then added to crushed-ice with stirring. The resulted precipitate was filtered off, dried and recrystallized from ethanol, Tables (1,2).

2-Alkyl amino-1,3,4-oxadiazole-5-thiol (7,8)[23]
4-Alkyl semicarbazide (3 or 4) (0.006 mole) was dissolved in alcoholic potassium hydroxide (0.4 g / 30 ml ethanol), to this solution carbon disulfide (8.0 ml) was added slowly, the mixture was refluxed for (16 h). The solvent was evaporated under reduced pressure, then

crushed-ice was added to the residue, and acidified with dilute hydrochloric acid. Compound (7) was formed as precipitate, which was filtered, dried and recrusyallized from ethanol, whereas compound (8) was isolated by the extraction of the mixture with ether (2 × 25 ml), the ester layer dried with magnesium sulfate and evaporated to give yellowish oily product, Tables (1,2).

2-Alkyl amino-5-amino-1,3,4-thiadiazole (9,10)[24]
A mixture of substituted 1-alkyl aminocarbonyl thiosemicarbazide (5 or 6) (0.005 mole) and concentrated sulfuric acid (9 ml) was stirred at room temperature for (1 hr) then heated with stirring on water bath at 90 °C for (2 hr). The mixture then poured on crushed ice, neutralized with concentrated ammonium hydroxide with cooling, the precipitate of compound (9) was filtered washed with cold water, dried and recrystallized from ethanol. While compound (10) was extracted by ether (2 × 25 ml), the ether layer was dried by magnesium sulfate, and evaporated under reduced pressure to give yellow oil, Tables (1,2).

5-Alkyl amino-1,3,4-(1H)triazole-2-thiol (11,12)[24]
A mixture of thiosemicarbazide (5 or 6) (0.005 mole) in sodium hydroxide solution (1%, 20 ml) was refluxed for (3 hr), the mixture was cooled and acidified with dilute hydrochloric acid, the precipitate was filtered off, washed with water, dried and recrystallized from ethanol-water, Tables (1,2).

4-Amino-5-alkyl amino-1,2,4-triazole-3-thiol (13,14)[25]
A mixture of substituted oxadiazole (7 or 8) (0.005 mole) and hydrazine hydrate (5 ml) in ethanol (20 ml), was refluxed for (6 h), then the solvent was evaporated under reduced pressure. The formed precipitate was filtered off, and recrystallized from ethanol, Tables (1,2).

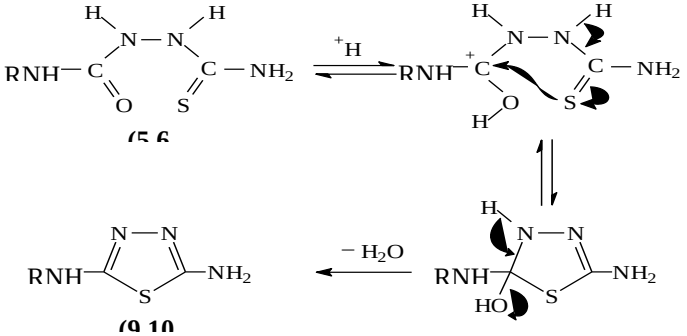
1-Amino-3,5-dialkyl amino-1,2,4-triazole (15)[26]
4-Alkyl semicarbazide (3) (0.002 mole, 0.314 g) was heated on sand bath at (90-120 °C) for (1 hr). Water (50 ml) was added and the mixture refluxed for (15 min.), the mixture then filtered, the precipitate dried and recrystallized from ethanol, Tables (1,2).

1, 2-Diamino-5-alkyl amino-1,3,4-triazole (16)[27]
A mixture of substituted 1-alkyl aminocarbonyl thiosemicarbazide (5) (0.005 mole) and hydrazine hydrate (5 ml, 0.1 mole) was refluxed for (2 h), the mixture was cooled, then poured on crushed ice, the solid formed was filtered off, washed with water, dried and recrystallized from ethanol, Tables (1,2).

Results and discussion

In the present work the synthesis of di and trisubstituted 1,2,4-triazoles and 3,5-disubstituted 1,3,4-oxadiazoles, 1,3,4-thiadiazoles is reported (Scheme 1). Cyclohexyl and hexyl amine were treated with methyl chloroformate to give Methyl-N-alkyl carbamate (1,2), the esters shows ν cm^{-1} at 1716-1710 (C=O), the esters then converted to the 4-alkyl semicarbazide (3,4) by their reaction with hydrazine hydrate in ethanol, the 4-alkyl semicarbazide (3,4) show ν cm^{-1} 3460, 3342 (N-H) and 1696-1682 (C=O). The 4-alkyl semicarbazide were treated with ammonium thiocyanates to give the corresponding 1-alkyl aminocarbonyl thiosemicarbazide (5,6), which show absorption at ν cm^{-1} 3316-3298 (N-H), 1673-1667 (C=O) and 1194-1186 (C=S).

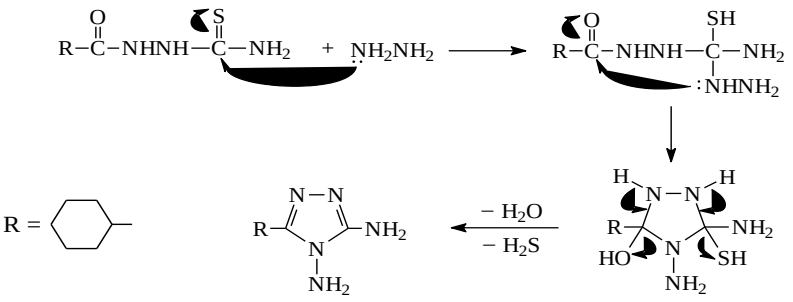
The 1-alkyl aminocarbonyl thiosemicarbazide (5,6) were converted to 2-alkyl amino-5-amino-1,3,4-thiadiazole (9,10) and 5-alkyl amino-1,2,4-triazole-3-thiol (11,12), by their reaction with concentrated sulfuric acid and sodium hydroxide respectively. The cyclization of substituted thiosemicarbazides to substituted 1,3,4-thiadiazole may pass through the following mechanism:



(5,6)

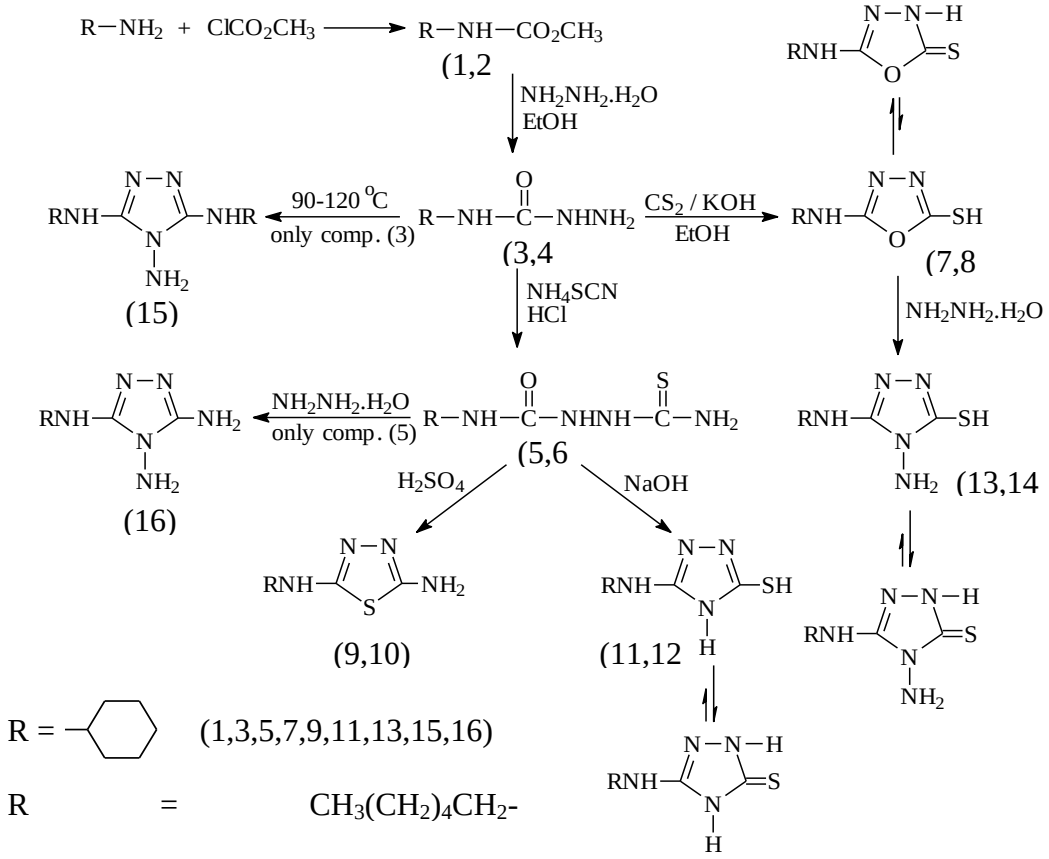
(9,10)

Whereas 1-cyclohexyl aminocarbonyl thiosemicarbazide (5) gave 3,4-diamino-5-cyclohexyl amino-1,2,4-triazole (16) by its reaction with hydrazine hydrate. The reaction mechanism is a follows:



The 2-alkyl amino-1,3,4-oxadiazole-5-thiol (7,8) were synthesized from 4-alkyl semicarbazide (3,4) by their reaction with carbon disulfide in alcoholic potassium hydroxide, the resulting substituted 1,3,4-oxadiazole were treated with hydrazine hydrate to give 4-amino-4-alkyl amino-1,2,4-triazole-3-thiol (13,14). Compound (3) was heated at (90-120 °C) to give 4-amino-3,5-dicyclohexyl amino-1,2,4-triazole (15).

The IR spectral data was show absorption at ν cm^{-1}: Compounds (7,8): 3325, 3290 (N-H), 1622, 1631 (C=N), 1244, 1228 (C=S) (of thione form). Compounds (9,10): 3375, 3282 (N-H), 1618, 1634 (C=N). Compounds (11,12): 3432, 3248 (N-H), 1210, 1192 (C=S), 1645, 1638 (C=N). Compounds (13,14): 3348, 3316 (N-H), 1208, 1186 (C=S), 1636, 1625 (C=N). Compound (15): 3320 (N-H) and 1642 (C=N). Compound (16): 3343 (N-H) and 1639 (C=N). The UV spectral data shows absorption peaks at λ_{max} 240-330 nm due to n→π* transition. The spectral and physical data of the prepared compounds are listed in Tables (1,2).



Scheme (1)

Table (1): Physical data of compounds (1-16)

Comp. No.	Molecular formula	m.p. °C	Yield %	Color
1	$C_8H_{15}NO_2$	74	67	White
2	$C_8H_{17}NO_2$	Oily	74	Pale yellow
3	$C_7H_{15}N_3O$	87-90	83	White
4	$C_7H_{17}N_3O$	Oily	80	Bright yellow
5	$C_8H_{16}N_4OS$	176	65	Pale brown
6	$C_8H_{18}N_4OS$	> 300	55	Light yellow
7	$C_8H_{13}N_3OS$	78-80	52	White
8	$C_8H_{15}N_3OS$	Oily	40	Yellow
9	$C_8H_{16}N_4S$	200 d	25	Yellowish brown
10	$C_8H_{16}N_4S$	Oily	60	Yellow
11	$C_8H_{14}N_4S$	163	68	Light yellow
12	$C_8H_{14}N_4S$	213-215	71	White
13	$C_8H_{15}N_5S$	157-159	54	White
14	$C_8H_{17}N_5S$	171-173	59	Light yellow
15	$C_{14}H_{26}N_6$	50-53	47	Yellow
16	$C_8H_{16}N_6$	120-123	51	Light yellow

Table (2): Spectral data of compounds (1-16)

Comp. No.	ν cm^{-1} (KBr)					UV EtOH λ_{max} (nm)
	N-H	C=O	C=S	C-O-C	C=N	
1	3345	1710	-	-	-	240
2	3340	1716	-	-	-	263
3	3342	1696	-	-	-	281
4	3460	1682	-	-	-	312
5	3298	1673	1194	-	-	294
6	3316	1667	1186	-	-	325
7	3325	-	1228	1091	1631	252
8	3290	-	1244	1110	1622	275
9	3375	-	-	-	1618	307
10	3282	-	-	-	1634	324
11	3432	-	1210	-	1645	298
12	3248	-	1192	-	1638	330
13	3316	-	1208	-	1625	256
14	3348	-	1186	-	1636	270
15	3320	-	-	-	1642	281
16	3343	-	-	-	1639	295

References

1. A. Saxena, R. Aron, S.C. Mehra and S.K. Tandam, Indian J. Pharm., 77 (1985) 113.
2. D. Lubermann, N. Rist and F. Grumbach, Congr. Intern. Biochim, 34 (1955) 136; Chem. Abstr., (1957), 51, 14137f.
3. Kowa, Co. Ltd., "2-B-Thenoylamido-1,3,4-thiadiazole", Jap., Kokai Pat., 8028 (1980) 946; Chem. Abstr., (1980), 93, 11453e.
4. H. Maradiya, J. Serb. Chem. Soc., 67 (2002) 11, 709.
5. F.X. Mathy, B. Vroman, D. Ntivunwa, A.J.D. Winne, R. Verbeeck and V. Preat, J. of Chromatography B., 787 (2003) 323.
6. S.S. Malsomoto, J.M. Fujitaki, L.D. Nord and R.C. Willis, Biochem. Pharmacol., 39 (1990) 455; Chem. Abstr., (1990), Vol. 112, 171869a.
7. E. Hoggarth, J. Chem. Soc., (1952) 4811.
8. R.W. Young and K.H. Wood, J. Am. Chem. Soc., 77 (1955) 400.
9. O.S. Moustafa, M.Z.A. Badr and T.I. EL-Emary, Bull. Korean Chem. Soc., 23 (2002) 4, 568.
10. A.O. Maslat, M. Abussad, H. Tashtoush and M. Al-Talib, Pol. J. Pharmacol., 54 (2002) 55.
11. J.D. Brooks, P.T. Charlton, P.E. Macey, D.A. Peak and W.F. Short, J. Chem., Soc., (1950) 454.
12. H.L. Yale and L. Kathryn, J. Med. Chem., 9 (1966) 478.
13. M. Hejsek and I. Wiedermannova, Chemica.,. 40 (2001) 16.
14. K.Y.D. AL-Zubaedi, M.Sc. Thesis, University of Mosul (1993).
15. M.S. Saeed, K.M. Bashi and F.B. AL-Dabbagh, Mutah J. for Research and Studies, 9 (1994) 189.
16. A. Varvareson, P.T. Siatra, T.A. Dalla and K.T. Santici, Farmco., 53 (1998) 320.
17. E. Alkerblom and K. Shagius, Acta Chem. Scand, 18 (1964) 174.
18. P.J. Kothari, V. Kishore V.I., Stenberg and S.S. Parmer, J. Heterocyclic Chem., 15 (1978) 1101.
19. M. Kiparir, A. Cetin and A. Cansiz, 10 (2005) 475.
20. S. Parrasion and G.A. Brieux, Bull. Soc. Chim. France, (1963) 35.
21. A. Shafiee, E. Naim, P. Mausobi, F.P. Foronmadi and M. Setrkari, J. Heterocyclic Chem., 32 (1995) 1235.
22. G.Y. Sarkis and F.S. Matti, Iraqi J. Chem., 10(1), (1991) 52.
23. E. Hoggarth, J. Chem. Soc., (1952) 4811.
24. M.S. Saeed, K.M. Bashi and F.B. Al-Dabbagh, Mu'tah Journal for Research and Studies, 9 (1994) 2, 189.
25. H.C. Brown, H.J. Gisler and M.T. Cheng, J. Org. Chem., 31 (1966) 781.
26. A.O. Mohammad, M.Sc. Thesis, (2001), University of Mosul.
27. U. Misra, A. Hitkari, A. Saxena, S. Gurtu and K. Shanker, Eur. J. Med. Chem., 31 (1996) 629.

تحضير عدد من معوضات الدايازول والترايازول من الامينات الاولية

خالد محمود داؤد و شيماء سمير اسماعيل

قسم الكيمياء، كلية التربية، جامعة الموصل، موصل، العراق

الخلاصة

تم في هذا البحث تحضير عدد من معوضات ٤،٣،١-اوكسادايازول و ٤،٣،١-ثايادايازول و ٤،٢،١-ترايازول. تم مفاعلة هكسيل حلقي امين وهكسيل امين مع كلوفورمات المثيل ليعطي N-الكيل كاربامات المثيل (٢،١) والتي تم تحويلها الى ٤-الكيل سيميكاربازيدات (٤،٣) من خلال مفاعلتها مع الهيدرازين المائي في الايثانول. حولت الهيدرازيدات الى معوضات الثايوسيميكاربازيدات (٦،٥) من خلال مفاعلتها مع ثايوسيانات الامونيوم / حامض الهيدروكلوريك المركز. تم مفاعلة الثايوسيميكاربازيدات (٦،٥) مع حامض الكبريتيك المركز او محلول هيدروكسيد الصوديوم ليعطي ٥-امينو-٢-مثيل امينو-٤،٣،١-ثايادايازول (١٠،٩) و ٥-مثيل امينو-٤،٢،١-ترايازول-٣-ثايول (١٢،١١) على التوالي. حول معوض الثايوسيميكاربازيد الى ٤،٣-ثنائي امينو-٥-هكسيل حلقي امينو-٤،٢،١-ترايازول (١٦) من خلال مفاعلته مع الهيدرازين. تم مفاعلة ٤-الكيل سيميكاربازيد مع ثنائي كبريتيد الكاربون في محلول هيدروكسيد الصوديوم ليعطي ٤،٣،١-اوكسادايازول المعوض. اعطت مفاعلة معوضات ٤،٣،١-اوكسادايازول مع الهيدرازين المائي معوضات ٤،٢،١-ترايازول (١٤،١٣)، بينما اعطى تسخين ٤-هكسيل سيميكاربازيد (٥) الى درجة ٩٠-١٢٠ °م ٤-امينو-٥،٣-ثنائي الكيل امينو-٤،٢،١-ترايازول (١٥). شخصت المركبات المحضرة بالطرق الطيفية والفيزياوية.