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RESEARCH ARTICLE

Synthesis of novel 2,3-condensed thieno[2,3-*d*]pyrimidin-4-ones via Appel's salt chemistry

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The chemistry of imino-1,2,3-dithiazoles possessing a thiophene ring with various alkyl and aromatic diamines was investigated in the expectation of obtaining novel 2,3-condensed thieno[2,3-*d*]pyrimidinone derivatives. Obtained via Appel's salt's (**1**) chemistry, methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-thiophenecarboxylate (**2**) is confirmed as a very interesting starting material for access to a variety of novel thiophene bioisosters of bioactive pentacyclic tetraaza-pentaphene-5, 8-diones.

Keywords: 4,5-Dichloro-1,2,3-dithiazolium chloride (Appel's salt); Microwave-assisted chemistry; Thiophene

1. Introduction

For more than a century, heterocycles have constituted one of the largest areas of research in organic chemistry. Their presence in numerous organic compounds of interest in biology, pharmacology, optics, electronics, material sciences, and so on is very well known. Among them, sulfur-containing heterocyclic compounds have maintained the interest of researchers and their unique structures have led to several applications in different areas [1]. Because thiophene is considered as a isoster of the benzene ring, we decided to explore the possibility of obtaining thiophene polyheterocyclic analogues of novel pentacyclic 5a,7a,13,14-tetraaza-pentaphene-5,8-diones [2] recently prepared by condensation of anthranilic acids with 4,5-dichloro-1,2,3-dithiazolium chloride **1** (Appel's salt) [3] and transformations of intermediate imines formed in that reaction [4, 5]. This work is a part of a research programme dealing with the preparation and pharmaceutical evaluation of sulfur and nitrogen-containing novel heterocycles for which interesting anticancer properties are expected [6, 7]. In this paper, we study the chemical behaviour of methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)thiophene-2-carboxylate **2** with alkanediamines which possess a variable length of the carbon chain

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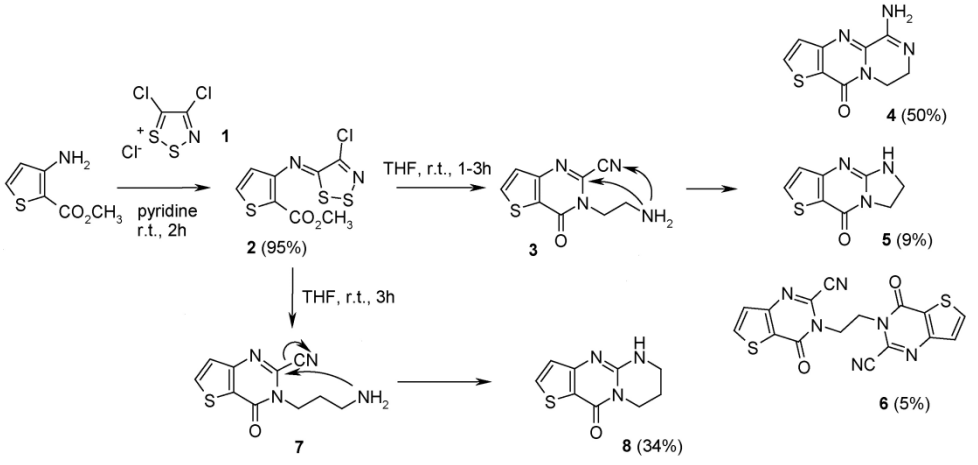
between the two functions. This strategy was also inspired by previous works of Kim and co-workers who have reported related reactions of similar intermediate benzene or thiophene based imines [8, 9]. Extending the potential applications of Appel's salt chemistry, we investigate the synthesis of novel 2,3-condensed thieno[2,3-*d*]pyrimidinones by condensation of aromatic or semi-aromatic diamines on the starting imino-1,2,3-dithiazoles.

2. Results and discussion

Following the usual methods [3, 8], treatment of methyl 3-amino-2-thiophenecarboxylate with 4,5-dichloro-1,2,3-dithiazolium chloride **1** in dichloromethane at room temperature gave the corresponding methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene) thiophene-2-carboxylate **2** in very good yield (95%). Expecting to vary the position of the sulfur atom on the targeted thiophenic derivatives, we tried to obtain the methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)thiophene-3-carboxylate counterpart. Unfortunately, no trace of the expected imine was detected.

It is now well known that condensation of aromatic amines and Appel's salt allows, in high yield, the synthesis of 5-(*N*-arylimino)-4-chloro-5*H*-1,2,3-dithiazoles [2]. These stable crystalline imines have proved to be highly versatile intermediates in heterocyclic synthesis and we have demonstrated that starting from anthranilic acid derivatives allows the synthesis of novel 2,3-condensed (3*H*)-quinazolin-4-ones, after opening of the dithiazole ring by alkanediamines [10].

Stirring of a solution of the imino-1,2,3-dithiazole **2** and ethylenediamine (1 equiv.) at room temperature in tetrahydrofuran, gave a mixture of two compounds **4** and **5** which could be separated by column chromatography and isolated as brown solids (scheme 1). The major product **4** then obtained was identified as the novel 5-amino-7,8-dihydro-1-thia-4,6,8a-triaza-cyclopenta[*b*]naphtalen-9-one for which the amidine isomerization in the solid state was suggested as it was demonstrated by X-ray crystallography for its benzene analogue [10]. The presence of a small amount of 6,7-dihydro-*5H*-imidazo[1,2-*a*]thieno[3,2-*d*]pyrimidin-8-one **5** (scheme 1) in the final products confirms existence of the intermediate *N*-substituted 4-oxo-3,4-dihydrothieno[3,2-*d*]pyrimidine-2-carbonitrile **3** which may cyclize by nucleophilic



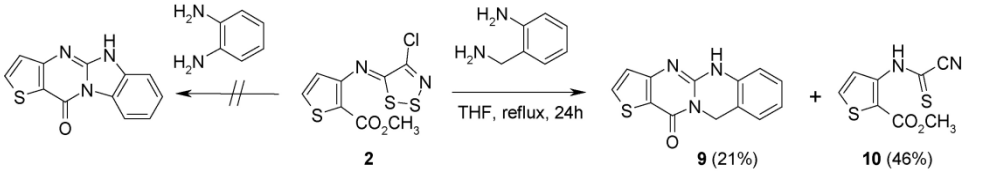
SCHEME 1 Reaction of **2** with alkanediamines.

attack of the primary amino group to the carbonitrile carbon or by nucleophilic displacement of the cyano group. Such a mechanism is confirmed by the results obtained by Kim's group which studied reaction of ethanolamine and compound **2** [8]. Scaling up the experiments (up to 0.5 g of starting material) led to the synthesis of a third product which was identified as the dimer **6**. The isolated quantity (5% yield), of this novel compound is low and very difficult to control. The parameters accounting for the presence of dimer **6** in the scaled-up experiments could not be successfully resolved.

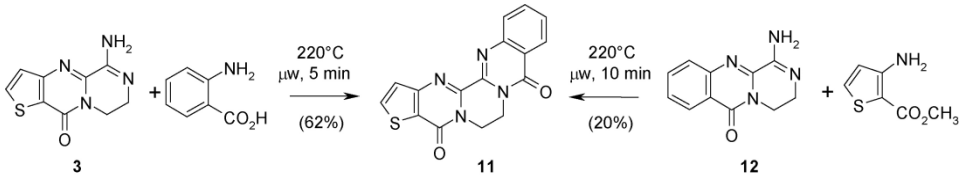
Extension of the carbon chain between the two amino groups was also explored. Reaction of compound **2** with 1,3-propanediamine was performed at room temperature and afforded only one cyclized product **8** which results from the substitution of the cyano group by nucleophilic attack of the aliphatic amine of the intermediate thienopyrimidinone **7**. This novel 5,6,7,8-tetrahydro-1-thia-4,5,8a-triaza-cyclopenta[*b*]naphtalen-9-one **8** was obtained in a yield of 34%, accompanied by an appreciable amount (15%) of the starting methyl 3-amino-2-thiophene carboxylate probably resulting from degradation of the imine **2**. In this case, no trace of dimer was observed even after an increasing of the quantities involved.

The second part of our work was directed toward extending the family of the amines studied to arene or semi-arene-diamines. Hence, we then decided to investigate the reaction of the imino-1,2,3-dithiazole **2** with *o*-phenylenediamine and *o*-aminobenzylamine. In these two reactants the distances between the two amines are similar to those observed with the aliphatic 1,2-ethanediamine or 1,3-propanediamines studied above. As described in preliminary studies on anthranilic analogues, the less nucleophilic *o*-phenylenediamine did not react with the starting iminodithiazole **2**. In contrast, *o*-aminobenzylamine possesses an aromatic amino group associated with a more nucleophilic alkylamino group. We discovered that long heating of imine **2** and *o*-aminobenzylamine in THF at reflux allowed the synthesis of a novel heterocyclic skeleton **9** in which the thienopyrimidine ring is fused with a quinazoline moiety, probably via an intermediate *N*-substituted thieno[3,2-*d*]pyrimidin-9-one which was not observed even at room temperature. The novel 5,10-dihydro-1-thia-4,5,10a-triaza-cyclopenta[*b*]anthracen-11-one **9** then obtained (21%) is accompanied by a large amount (46% yield) of the unexpected cyanothioformamide **10** which may result from two nucleophilic attack of aliphatic amines on S-2 of the imino-1,2,3-dithiazole ring, in a mechanism previously described for benzene derivatives [4, 8, 11].

Exploring the potential synthetic applications of the Niementowski reaction [12] and in association with our work on the use of microwaves for the synthesis of bioactive molecules [13, 14], we planned to fuse the thieno[3,2-*d*]pyrimidin-9-one and the quinazoline rings. Microwave irradiation under pressure [15, 16] at 220°C of a mixture of amidine (**3**) and an excess of anthranilic acid (4 equiv.) in the presence of graphite (10% by weight), gave the novel 5,6-dihydro-3-thia-4a,6a,12,13-tetraaza-indeno[5,6-*a*]anthracene-4,7-dione **11** in good yield. The strong thermal effect due to graphite/microwaves interaction [15] is particularly efficient in this condensation reaction which needs high temperatures and requires lengthy and tedious traditional conditions.



SCHEME 2 Reaction of **2** with aromatic or semi-aromatic amines.



SCHEME 3 Microwave assisted syntheses of compound **11**.

Searching for the most efficient route for a possible extension of this process to a library of new bioactive compounds, we investigated the condensation of amidine **12** (described in [2]) with methyl 2-amino-3-thiophenecarboxylate. The attempted molecule **11** was obtained with a low yield (20%), accompanied by miscellaneous degradation products.

3. Experimental

Commercial reagents were used as received without additional purification. Melting points were measured using a Kofler melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Paragon 1000PC FT-IR instrument. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded with a JEOL JNM LA400 spectrometer. Chemical shifts (δ values) are expressed in parts per million downfield from tetramethylsilane as an internal standard and coupling constants (J) are expressed in Hertz. Thin-layered chromatography (TLC), was performed on 0.2 mm precoated plates of silica gel 60F-264 (Merck). Visualisation was made with ultraviolet light. Column chromatography was performed by using Merck silica gel (70–230 mesh). High-resolution mass measurements were performed on a Varian MAT 311 in the *Centre Régional de Mesures Physiques de l'Ouest* (*CRMPO, Université de Rennes*).

The microwave heating was performed in an Smith-Synthetizer^{TM} (Personal Chemistry, AB) single mode cavity, producing controlled irradiation at 2450 MHz (detailed description of this microwave reactor with integrated robotics was recently published [17]. Reaction temperature and pressure were determined using the built-in, on-line IR and pressure sensors. Microwave assisted reactions were performed in sealed Smith process vials (0.5–5 mL, total volume 10 mL) under air with magnetic stirring. The software algorithm regulates the microwave output power so that the selected maximum temperature was maintained for the desired reaction/irradiation time. After the irradiation period, the reaction vessel was cooled rapidly to ambient temperature by compressed air (gas-jet cooling). The minimal reaction times were determined by performing sequential series of identical reactions at constant temperature and with continuous heating, but with different irradiation times. Completion of the reaction was estimated by TLC after each individual heating period.

3.1 *Synthesis of compounds (4), (5), (6) and (8) from ester (2)*

A solution of methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-yliden)-3-amino-thiophene-2-carboxylate (**2**) (0.5 g, 1.71 mmol) in tetrahydrofuran (10 mL, THF) was added slowly to a solution of ethylenediamine (0.11 mL, 1.71 mmol) in THF (10 mL). The mixture was stirred for 3 h at room temperature under inert atmosphere (argon). After evaporation of the solvent under reduced pressure, column chromatography on silica gel (dichloromethane/ethyl acetate, 8:2) gave products (**4**) (50%), (**5**) (9%) and (**6**) (5%) as solids.

3.2 *5-Amino-7,8-dihydro-1-thia-4,6,8a-triaza-cyclopent[b]naphthalen-9-one (4)*

Brown solid; mp 192°C; IR (KBr) ν 784, 1698, 1742, 2966, 3246, 3444 cm^{-1}; ^1H NMR (d_6-DMSO + D_2O) δ 3.59 (t, $J = 5.6$ Hz, 2H), 4.06 (t, $J = 5.6$ Hz, 2H), 7.47 (d, $J = 5.4$ Hz, 1H), 8.23 (d, $J = 5.4$ Hz, 1H); ^{13}C NMR (d_6-DMSO + D_2O) δ 38.44, 42.55, 122.98, 125.25, 135.78, 141.72, 151.40, 154.65, 156.00; MS (EI) m/z = 220 (M^+); HRMS: calcd for $C_9H_8N_4OS$, 220.0419; found, 220.0408.

3.3 *6,7-Dihydro-5H-imidazo[1,2-a]thieno[3,2-d]pyrimidin-8-one (5)*

Brown solid; mp 172°C decomp.; IR (KBr) ν 781, 1077, 1523, 1627, 1681, 2898, 3096 cm^{-1}; ^1H NMR (d_6-DMSO + D_2O) δ 3.67 (t, $J = 8.4$ Hz, 2H), 4.13 (t, $J = 8.4$ Hz, 2H), 7.02 (d, $J = 5.2$ Hz, 1H), 7.23 (d, $J = 5.20$ Hz, 1H); ^{13}C NMR (d_6-DMSO + D_2O) δ 40.42, 42.79, 113.07, 124.04, 135.00, 157.38, 157.89, 160.11; MS (EI) m/z = 193 (M^+); HRMS: calcd for $C_8H_7N_3OS$, 193.0310; found, 193.0306.

3.4 *Bis-3-methylene-4-oxo-3,4-dihydro-thieno[3,2-d]pyrimidine-2-carbonitrile (6)*

White solid; mp > 260°C; IR (KBr) ν 785, 1179, 1453, 1552, 1708, 2245, 3121 cm^{-1}; ^1H NMR (d_6-DMSO) δ 4.70 (s, 4H), 7.55 (d, $J = 5.6$ Hz, 2H), 8.33 (d, $J = 5.6$ Hz, 2H); ^{13}C NMR (d_6-DMSO) δ 45.11, 112.04, 125.74, 125.87, 133.30, 138.17, 155.03, 156.38; MS (EI) m/z = 380 (M^+); HRMS: calcd for $C_{16}H_8N_6O_2S_2$, 380.0150; found, 380.0184.

Compound **8** was prepared in a yield of 34%, as described below for **4**, **5** and **6** by condensation of 1,3-diaminopropane (0.09 mL, 1.03 mmol) with ester **2** (0.3 g, 1.03 mmol) in THF (10 mL).

3.5 *5,6,7,8-Tetrahydro-1-thia-4,5,8a-triaza-cyclopenta[b]naphthalen-9-one (8)*

Brown solid; mp > 260°C; IR (KBr) ν 538, 782, 1060, 1535, 1678, 2943 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05–2.15 (m, 2H), 3.50 (t, $J = 6.0$ Hz, 2H), 4.12 (t, $J = 6.0$ Hz, 2H), 5.90 (s, 1H), 6.92 (d, $J = 5.4$ Hz, 1H), 7.63 (d, $J = 5.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.47, 39.52, 39.62, 112.81, 122.98, 134.30, 151.97, 157.76, 158.13; MS (EI) m/z = 207 (M^+); HRMS: calcd for $C_9H_9N_3OS$: 207.0466; found, 207.0469.

3.6 *Synthesis of compounds (9) and (10) from ester (2)*

A solution of ester (**2**) (0.35 g, 1.20 mmol) and 2-aminobenzylamine (0.29 g, 2.40 mmol) in THF (20 mL) was heated at reflux for 24 h. Upon cooling, the solvent was evaporated off and the residue was purified by column chromatography on silica gel (dichloromethane/ethyl acetate, 8:2) to furnish **9** (21%) and **10** (46%).

3.7 *5,10-Dihydro-1-thia-4,5,10a-triaza-cyclopenta[b]anthracen-11-one (9)*

White solid; mp > 260°C; IR (KBr) ν 757, 1446, 1472, 1525, 1673, 3271 cm^{-1}; ^1H NMR (d_6-DMSO) δ 5.14 (s, 2H) 6.94–7.00 (m, 2H) 7.08 (d, $J = 5.2$ Hz, 1H), 7.17–7.24 (m, 1H) 7.29 (d, $J = 7.6$ Hz, 1H), 8.03 (d, $J = 5.2$ Hz, 1H), 10.29 (s, 1H, NH); ^{13}C NMR (d_6-DMSO) δ 42.71, 114.29, 114.38, 116.98, 122.43, 124.13, 126.86, 128.86, 135.73, 136.33, 149.38, 157.61, 158.01; MS (EI) m/z = 255 (M^+); HRMS: calcd for $C_{13}H_9N_3OS$: 255.0466; found, 255.0467.

3.8 *3-(Cyanocarbothioyl-amino)-thiophene-2-carboxylic acid methyl ester (10)*

Red solid; mp 115°C; IR (KBr) ν 1115, 1277, 1571, 1678, 2226 (CN), 2958, 3186 cm^{-1}; ^1H NMR ($CDCl_3 + D_2O$) δ 3.98 (s, 3H), 7.60 (d, $J = 6.0$ Hz, 1H), 8.77 (d, $J = 6.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 52.81, 113.69, 116.10, 122.05, 131.69, 143.10, 160.74, 164.37; MS (EI) m/z = 226 (M^+); HRMS: calcd for $C_8H_6N_2O_2S_2$: 225.9871; found, 225.9890.

3.9 *Synthesis of 5,6-dihydro-3-thia-4a,6a,12,13-tetraaza-indeno[5,6-a]anthracene-4,7-dione (11)*

A mixture of amidine **3** (0.06 g, 0.26 mmol), anthranilic acid (0.14 g, 1.04 mmol) dispersed with graphite (10% by weight: 0.02 g) was introduced in a pressure-rate reaction tube. The tube was irradiated at 220°C for 5 min. After cooling, the graphite powder was filtered off and washed with dichloromethane. The solution was washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$) and concentred under reduced pressure. Purification by column chromatography on silica gel (dichloromethane/ethyl acetate, 9:1) afforded product **11** in a yield of 62%.

Brown solid; mp > 260°C ; IR (KBr) ν 784, 1152, 1471, 1602, 1676, 2906, 3076 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.58–4.60 (m, 4H), 7.64 (t, $J = 8.0$ Hz, 1H), 7.67 (d, $J = 5.6$ Hz, 1H) 7.85–7.90 (m, 1H), 7.91 (d, $J = 5.6$ Hz, 1H), 8.09 (d, $J = 8.0$ Hz, 1H) 8.38 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 38.77, 38.88, 121.19, 124.00, 126.63, 126.94, 129.02, 129.41, 135.07, 135.24, 143.22, 144.91, 147.04, 156.17, 160.17; MS (EI) $m/z = 322$ (M^+); HRMS: calcd for $C_{16}H_{10}N_4O_2S$: 322.0525; found, 322.0519.

4. Conclusion

In conclusion, the work described in this paper is a further example of the utility of Appel's salt in the conception of novel heterocyclic rings. Confirming previous works, we observed that methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-thiophenecarboxylate (**2**) is a very interesting starting material for the access to various 2,3-condensed thieno[3,2-*d*] pyrimidinone derivatives themselves precursors of novel thiophene isosters of pentacyclic tetraaza-pentaphene-5,8-diones derivatives. Application of microwave technology for the synthesis of a library of various sulfur and nitrogen-containing molecules is under investigation and will be published later, accompanied by their biological evaluation.

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