Tetrahedron Letters 56 (2015) 1011–1014

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Access to newly functionalized imidazole derivatives: efficient synthesis of novel 5-amino-2-thioimidazoles using propylphosphonic anhydride (®T3P)

Manuel Lasalle [a,b], Sylvain Picon [a,b], Rajaa Boulahjar [a,b], Vanessa Hoguet [a,b], Jolien Van Obbergen [c], Pascal Roussel [d], Benoit Deprez [a,b], Julie Charton [a,b,*]

[a] Biostructures and Drug Discovery, INSERM U761, Institut Pasteur de Lille, Université de Lille, Lille F-59000, France
[b] PRIM, Lille F-59000, France
[c] Faculty of Pharmaceutical Sciences, Ghent University, B-9000 Ghent, Belgium
[d] Unité de Catalyse et Chimie du Solide (UCCS), CNRS UMR 8181, Ecole Nationale Supérieure de Chimie de Lille, Université Lille Nord de France, Villeneuve d'Ascq F-59652, France

ARTICLE INFO

Article history:
Received 1 December 2014
Revised 23 December 2014
Accepted 6 January 2015
Available online 12 January 2015

Keywords:
Aminothioimidazole
Propylphosphonic anhydride (®T3P)
Microwave

ABSTRACT

We describe here an efficient method to synthesize 5-amino-2-thioimidazole compounds by T3P-mediated cyclization of *N*-acetamidoisothiourea intermediates. The newly functionalized 5-amino-2-thioimidazole compounds are finally obtained in 5 steps from an amine as starting block.

Imidazoles represent an important family of heterocycles and are incorporated in many compounds of both chemical and biological interest. In particular a large number of imidazole-based drugs including anticancer (dacarbazine), antibacterial, antiparasitic (metronidazole), antifungal (ketoconazole), anxiolytic, and sedative (midazolam), antihistaminic (cimetidine), and antihypertensive (losartan) agents are widely used. The high therapeutic properties of imidazole related drugs have encouraged the medicinal chemists to synthesize and test a large number of new imidazole derivatives.[1] Additional improvements in the biological activities can be further achieved by small modifications in the substituents on the imidazole core. 2-Aminoimidazole (Fig. 1) has been described as a privileged pharmacophore and a scaffold of interest for the preparation of high value small molecules for medicinal chemistry.[2] 2-Thioimidazoles (Fig. 1) are present in COX-2 selective inhibitors,[3] CCR2 antagonists,[4] H3 antagonists,[5] and in compounds that possess antitubercular activity.[6]

Interestingly, only very few 5-aminoimidazole[7] (Fig. 1) compounds and their synthetic methods are reported in the literature. Moreover, while isosteric replacement is a common strategy in medicinal chemistry, only very few 5-amino-2-thioimidazoles coming from either carbon-to-nitrogen replacement on 2-thioimidazole compounds or carbon-to-sulfur replacement on 5-aminoimidazole compounds have been described. In 1980, the synthesis of six 2-thio-5-morpholinoimidazole compounds was published.[8] More recently the preparation of one 5-amino-2-thioimidazole compound starting from an *N*-acetamidoisothiourea intermediate was reported.[9] The 5-amino-2-thioimidazole was obtained in two steps with a moderate yield of 39% (Fig. 2).

Herein, we report a one step procedure for the preparation of original 5-amino-2-thioimidazole derivatives starting from acetamidoisothiourea intermediates using ®T3P (propylphosphonic anhydride)[10] for the cyclodehydration step.

®T3P is a powerful water scavenger and coupling reagent initially used for amide synthesis. Because of the low toxicity, high safety, and ease of handling of this reagent, it has in recent years been used for many other applications.[11] In particular the synthetic utility of this reagent as a cyclodehydration agent has been described for the synthesis of various heterocycles such as oxadiazoles and thiadiazoles,[12] benzothiazoles, benzoxazoles, and benzimidazoles.[13]

The cyclization of the *N*-acetamidoisothiourea intermediate in 5-amino-2-thioimidazole using T3P was examined with compound **1c** as a prototype starting material to optimize the reaction conditions. Compound **1c** was obtained starting from *N*-methylaniline,

* Corresponding author. Tel.: +33 3 20964928; fax: +33 3 20964709.
E-mail address: julie.charton@univ-lille2.fr (J. Charton).

http://dx.doi.org/10.1016/j.tetlet.2015.01.046
0040-4039/

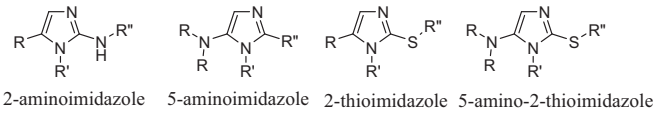


Figure 1. Structures of imidazole derivatives.

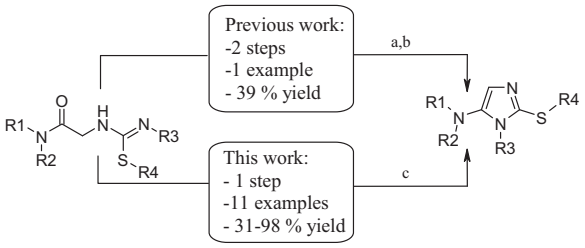
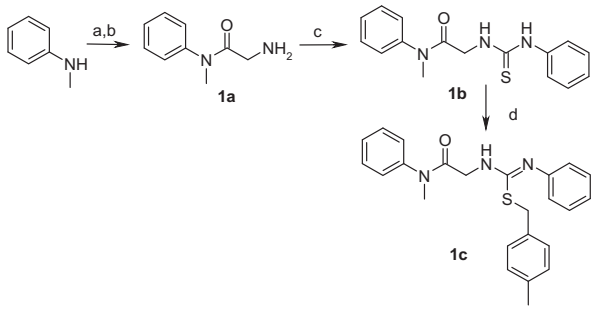


Figure 2. 2-Step synthesis of 5-amino-2-thioimidazole from *N*-acetamidoisothiourea precursor versus one step procedure using T3P. ((a) Lawesson's reagent, 1,2-dimethoxyethane, 20 °C, 16 h, (b) 4 N NaOH, 20 °C, (c) T3P, DIEA, EtOAc, microwave or classical heating.)



Scheme 1. (a) Chloroacetyl chloride, DIEA, DCM, 0 °C, (b) aq NH_3, EtOH, 65 °C, (c) phenylisothiocyanate, TEA, EtOH, rt, (d) 1-bromomethyl-4-methylbenzene, NaI, K_2CO_3, acetonitrile, rt.

which was first acylated with chloroacetyl chloride in dichloromethane in the presence of DIEA as the base (Scheme 1). The chlorine atom was then substituted by aqueous ammonia in ethanol to give the amino intermediate **1a**. Compound **1a** was reacted with the appropriate isothiocyanate to give the thiourea **1b** which was then selectively alkylated on the sulfur atom with 1-bromomethyl-4-methylbenzene to give the precursor for the cyclization **1c**. Single crystal X-ray diffraction confirmed the S-alkylation of compound **1c**.

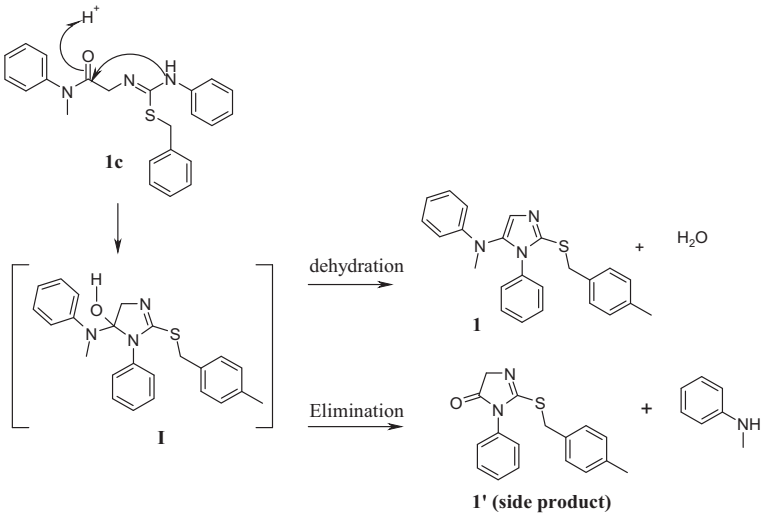
Table 1
Optimization of conditions for synthesis of **1**

Entry	T3P (equiv)	DIEA (equiv)	*T* (°C)	Time	% **1** (% **1′**) [a,b]
Classical heating					
1	1	2	Reflux	2 h	2 (2)
2	1	2	Reflux	4 h	4 (13)
3	1	2	Reflux	8 h	5 (40)
4	1	2	Reflux	24 h	9 (83)
5	0	2	Reflux	24 h	0 (0)
6	3	6	Reflux	2 h	23 (nd)
7	3	6	Reflux	4 h	30 (nd)
8	3	6	Reflux	8 h	48 (2)
9	3	6	Reflux	24 h	63 (6)
10	3+3[c]	6+6[c]	Reflux	24 h	80 (nd)
Microwave heating					
11	1	1	100	10 min	13 (8)
12	1	1	100	20 min	14 (9)
13	2	4	100	10 min	12 (nd)
14	2	4	100	20 min	21 (nd)
15	2	4	120	10 min	65 (9)
16	2	4	120	20 min	79 (14)
17	2	4	130	20 min	86 (11)
18	2	4	150	10 min	88 (12)
19	3	6	150	10 min	96 (4)
20	3	4.5	150	10 min	95 (5)
21	3	3	150	10 min	90 (10)
22	1	2	150	10 min	62 (33)

[a] Determined by LC–MS at 215 nm.
[b] nd: not detected.
[c] Additional equivalent of T3P (3 equiv) and DIEA (6 equiv) are added after 8 h of reaction.

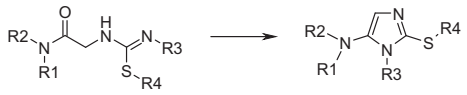
We first tried the reaction under classical heating starting from **1c** with T3P (1 equiv) and DIEA (2 equiv) in ethyl acetate, a classical solvent for the use of T3P. Under these conditions, we could observe the formation of the desired product (**1**) but a side product (**1′**) appeared mainly in the reaction mixture after 24 h (Table 1, entry 4). This undesired product results from the elimination of the aniline moiety instead of the expected dehydration (Scheme 2).

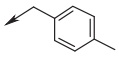
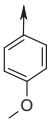
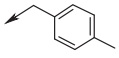
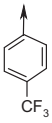
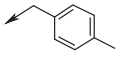
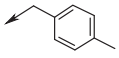
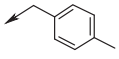
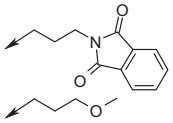
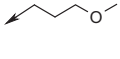
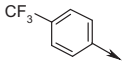
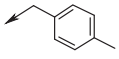
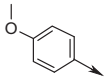
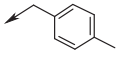
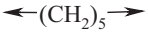
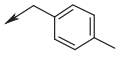
As T3P is known as a dehydration agent, we hypothesized that an increase in T3P quantity could favor the dehydration step



Scheme 2. Proposed mechanism for the formation of 5-amino-2-thioimidazole **1** and side product **1′**.

Table 2
Scope of the 5-amino-2-thioimidazole synthesis



Compd	R1	R2	R3	R4	Yield (%)
1	CH_3				58
2	CH_3				71
3	CH_3				75
4	CH_3				98
5	CH_3				51
6	CH_3			$-CH_3$	77
7	CH_3				61
8	CH_3				92
9	CH_3				70
10	CH_3				50
11					31

instead of aniline elimination. The effect of the stoichiometry of T3P was further investigated. As shown in Table 1 (entries 6–9), increasing the amount of T3P to 3 equiv allowed a marked increase in **1**:**1**′ ratio (63:6 after 24 h, entry 9). The addition of T3P (3 equiv) and DIEA (6 equiv) after 8 h of reaction (entry 10) led to a 80% conversion rate (after 24 h) without detection of the undesired compound **1**′.

Eventually, in order to validate that the cyclization was mediated by T3P and not just by a thermal process in basic media, a control experiment without T3P (entry 5) was undertaken. No conversion was observed, confirming the importance of T3P in the reaction. Moreover, experiments using dehydrating agents like acetic anhydride and trifluoroacetic anhydride failed to provide the target compound (data not shown).

With the aim to reduce reaction time, we then carried out the reaction under microwave irradiation. Comparable to classical heating, the conversion of **1c** into **1** increased with the amount of T3P (entry 11 vs 13, 12 vs 14). Then the effect of the temperature was investigated (entries 14, 16, and 17 for 10 min reaction and 15 and 18 for 20 min reaction). An increase in temperature led to improved conversion and 150 °C was chosen for further optimization. At this temperature, a decrease of the amount of DIEA (entries 20 and 21) or in T3P (entry 22) was detrimental for the conversion.

T3P (3 equiv), DIEA (6 equiv) under microwave heating at 150 °C during 10 min appeared optimal for the conversion of the reaction (entry 19).

The optimized conditions (Table 1, entry 19) were then used to explore the scope of the reaction. We investigated the effect of each substituent (R1–R4, Table 2).[14]

In R3, both aryl (**1**–**4**) and alkyl groups (**5**) were compatible with the reaction. Hindered aromatic rings in R3 were well tolerated (**4**, 98% yield). The presence of electron withdrawing or donating groups on the aromatic ring in R3 position (**2**–**3**) had no impact on the yield of the reaction. Influence of the sulfur component (R4) was assessed using aliphatic (**6**–**8**) or benzylic (**1**) groups. An ether function (**8**) as well as a protected amine (phthalimide protection, **7**) did not impact the reaction. Finally, the influence of the substitution on the nitrogen atom (R1, R2) was evaluated. *N*-Methylaniline bearing electron withdrawing or donating groups were tested. The yield was better (70%) in the case of *para*-CF3 substitution (**9**) compared to *para*-OMe (**10**, 50%) or the unsubstituted aromatic ring (**1**, 58%). The electron withdrawing effect of the CF3 group is likely to enhance the electrophilicity of the carbonyl of the amide function thereby facilitating the nucleophilic attack by the nitrogen of the isothiourea moiety. Conversely, the methoxy electron donating group decreases the reactivity of the carbonyl compared to the unsubstituted aromatic ring. The piperidine was evaluated as an aliphatic amine and gave the desired compound in a moderate yield of 31%. In this case, the elimination of the piperidine instead of the dehydration was also observed leading to the side product **1**′ (60% yield).

In summary, a method for the synthesis of original 5-amino-2-thioimidazoles has been developed. This method takes advantage of a highly selective T3P-mediated microwave cyclodehydration of *N*-acetamidoisothiourea and yields the target imidazoles in good to excellent yields. This novel access to an underrepresented class of imidazoles could be of high interest in medicinal chemistry.

Acknowledgments

We are grateful to the institutions that support our laboratory: INSERM, Université de Lille, Institut Pasteur de Lille. This project was supported by Conseil Régional Nord-Pas de Calais, EDFR (convention 11003609), Etat DRRT, PRIM and Université Lille 2 (Appel à projets «orientations stratégiques»: convention A007). Manuel Lasalle is a recipient of a doctoral fellowship of the French Ministere de la Recherche. NMR acquisitions were done at the Laboratoire d'Application de Résonance Magnétique Nucléaire (LARMN), Lille, France.

Supplementary data

Crystallographic data (including structure factors) for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC1029533. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.Uk).

Supplementary data (detailed synthesis, spectral data for all compounds and RX data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.01.046.

References and notes

1. (a) Zhang, L.; Peng, X.-M.; Damu, G. L. V.; Geng, R.-X.; Zhou, C.-H. *Med. Res. Rev.* **2014**, *34*, 340–437; (b) De Luca, L. *Curr. Med. Chem.* **2006**, *13*, 1–23.
2. Sullivan, J. D.; Giles, R. L.; Looper, R. E. *Curr. Bioact. Compd.* **2009**, *5*, 39–78.
3. Navidpour, L.; Shadnia, H.; Shafaroodi, H.; Amini, M.; Dehpour, A. R.; Shafiee, A. *Bioorg. Med. Chem.* **2007**, *15*, 1976–1982.
4. Van Lommen, G.; Doyon, J.; Coesemans, E.; Boeckx, S.; Cools, M.; Buntinx, M.; Hermans, B.; Jean, V. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 497–500.
5. Jablonowski, J. A.; Ly, K. S.; Bogenstaetter, M.; Dvorak, C. A.; Boggs, J. D.; Dvorak, L. K.; Lord, B.; Miller, K. L.; Mazur, C.; Wilson, S. J.; Lovenberg, T. W.; Carruthers, N. I. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 903–907.
6. Fassihi, A.; Azadpour, Z.; Delbari, N.; Saghaie, L.; Memarian, H. R.; Sabet, R.; Alborzi, A.; Miri, R.; Pourabbas, B.; Mardaneh, J.; Mousavi, P.; Moeinifard, B.; Sadeghi-aliabadi, H. *Eur. J. Med. Chem.* **2009**, *44*, 3253–3258.
7. Kim, O.; Jeong, Y.; Lee, H.; Hong, S.-S.; Hong, S. *J. Med. Chem.* **2011**, *54*, 2455–2466.
8. Meola, S.; Rivera, E.; Stradi, R.; Gioia, B. *J. Heterocycl. Chem.* **1980**, *17*, 1041–1044.
9. Lamberth, C.; Dumeunier, R.; Trah, S.; Wendeborn, S.; Godwin, J.; Schneiter, P.; Corran, A. *Bioorg. Med. Chem.* **2013**, *21*, 127–134.
10. T3P is a registered trademark of Archimica.
11. (a) Meudt, A.; Scherer, S.; Boehm, C. U.S. Patent 20070191645A1, 2007.; (b) Zumpe, F. L.; Flüß, M.; Schmitz, K.; Lender, A. *Tetrahedron Lett.* **2007**, *48*, 1421–1423; (c) Augustine, J. K.; Atta, R. N.; Ramappa, B. K.; Boodappa, C. *Synlett* **2009**, 3378–3382; (d) Crawforth, J. M.; Paoletti, M. *Tetrahedron Lett.* **2009**, *50*, 4916–4918; (e) Narendra, B. N.; Lamani, R. S.; Sureshbabu, V. V. *Tetrahedron Lett.* **2010**, *51*, 3002–3005; (f) Scaravelli, F.; Bacchi, S.; Massari, L.; Curcuruto, O.; Westerduin, P.; Maton, W. *Tetrahedron Lett.* **2010**, *51*, 5154–5156; (g) Augustine, J. K.; Kumar, R.; Bombrun, A.; Mandal, A. B. *Tetrahedron Lett.* **2011**, *52*, 1074–1077; (h) Augustine, J. K.; Bombrun, A.; Venkatachaliah, S. *Tetrahedron Lett.* **2011**, *52*, 6814–6818; (i) Desroses, M.; Wieckowski, K.; Stevens, M.; Odell, L. R. *Tetrahedron Lett.* **2011**, *52*, 4417–4420; (j) Augustine, J. K.; Bombrun, A.; Alagarsamy, P.; Jothi, A. *Tetrahedron Lett.* **2012**, *53*, 6280–6287; (k) Augustine, J. K.; Bombrun, A.; Ramappa, B.; Boodappa, C. *Tetrahedron Lett.* **2012**, *53*, 4422–4425; (l) Madhu, C.; Basavaprabhu; Vishwanatha, T. M.; Sureshbabu, V. V. *Tetrahedron Lett.* **2012**, *53*, 1406–1409; (m) Nagendra, G.; Madhu, C.; Vishwanatha, T. M.; Sureshbabu, V. V. *Tetrahedron Lett.* **2012**, *53*, 5059–5063; (n) Poojari, S.; Parameswar Naik, P.; Krishnamurthy, G. *Tetrahedron Lett.* **2012**, *53*, 4639–4643; (o) Sharnabai, K. M.; Nagendra, G.; Vishwanatha, T. M.; Sureshbabu, V. V. *Tetrahedron Lett.* **2013**, *54*, 478–482.
12. Augustine, J. K.; Vairaperumal, V.; Narasimhan, S.; Alagarsamy, P.; Radhakrishnan, A. *Tetrahedron* **2009**, *65*, 9989–9996.
13. Wen, X.; El Bakali, J.; Deprez-Poulain, R.; Deprez, B. *Tetrahedron Lett.* **2012**, *53*, 2440–2443.
14. Typical procedure for the preparation of the 5-amino-2-thioimidazole derivatives (**1** as example). In two microwave tubes were introduced compound **1c** (0.62 mmol, 2 × 125 mg), ethyl acetate (0.1 M, 2 × 3 mL), DIEA (3.7 mmol, 2 × 325 μL) and T3P (50% in EtOAc, 1.85 mmol, 2 × 547 μL). The mixtures were heated with microwave at 150 °C for 10 min. Then, both reaction mixture were pooled together, diluted with ethyl acetate, and washed with saturated sodium bicarbonate and brine. The organic phase was dried over sodium sulfate and evaporated to dryness. The crude product was purified by flash chromatography (cyclohexane/ethyl acetate) to give *N*-methyl-2-{[(4-methylphenyl)methyl]sulfanyl}-*N*,1-diphenyl-1*H*-imidazol-5-amine **1** (137 mg, 58% yield) as pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.28 (m, 3H), 7.09 (t, 6H), 7.01 (s, 1H), 6.97–6.94 (m, 2H), 6.67 (t, J = 7.5 Hz, 1H), 6.51 (d, J = 7.8 Hz, 2H), 4.17 (s, 2H), 2.95 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 148.4, 139.9, 138.2, 137.1, 134.9, 134.2, 129.2, 129.0, 128.9, 128.7, 127.4, 124.6, 118.5, 113.5, 39.4, 38.2, 21.2. LC–MS: t_R = 3.55 min, m/z = 386 = $[M+H]^+$ HRMS: calcd for $C_{24}H_{24}N_3S$, (MH+) 386.1691, found 386.1696.