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Easy access to triazoles, triazolopyrimidines, benzimidazoles and imidazoles from imidates

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ABSTRACT

We have described a new and easy synthesis of triazoles, triazolopyrimidines, benzimidazoles and imidazoles variously substituted based on the reaction of imidates with diamine derivatives. The products were obtained in moderate to good yields. A general mechanism for the reactions is proposed.

The study of heterocyclic systems of triazole, triazolopyrimidine, benzimidazole and imidazole type has known a considerable development due to the revealing of their varied effects in diverse domains. These last years, research become intensified and turned to the synthesis of this kind of compounds[1] and the study of their activities in the pharmacological and agrochemical fields.

Indeed, these compounds are widely used in agricultural chemistry as herbicides[2] and in the biosynthesis of chlorophylls.[3] They are known for their antitumoral,[4] antibiotic,[2a] antifungal[2a,5] and antibacterial[5] properties. They also present inhibitive properties of corrosion of metals.[6]

Owing to all these real and potential properties we established a research program that focussed on the synthesis of new triazoles and triazolopyrimidines, and resulted in the discovery of a simple and general route for the preparation of 3-amino-1,2,4-triazoles and 7-amino-1,2,4-triazolopyrimidines starting from the corresponding imidates **1** and **2**.

Indeed, the bis electrophilic character of easily accessible imidates[7] **1** and **2** would allow to postulate that their reaction with the hydrazine derivatives could constitute an easy access to new series of 3-amino-1,2,4-triazoles **3**.

When a variety of imidates **1** or **2** were treated with hydrazine derivatives, good yields of 3-amino-1,2,4-triazoles **3** was obtained (Scheme 1). The typical experimental procedure is outlined in Ref. 8. The yields of these reactions are collected in Table 1.

All triazoles **3** were characterized by satisfactory HRMS and by NMR spectroscopy.[8]

Scheme 1 depicts a mechanism which shows the formation of 3-amino-1,2,4-triazoles **3**. This reaction is comparable to mechanisms described in the literature.[9]

The reaction was assumed to proceed by substitution of the ethoxy group of **1** or **2** with the hydrazines giving intermediates **4** or **5**, which then immediately yield 1,2,4-triazoles **3** by reaction of heterocyclisation.

In order to confirm the mechanism, we verified that the thermolysis of amidrazones **5**, which we isolated by an independent way,[10] in methanol gives exclusively 3-amino-1,2,4-triazoles **3** (Scheme 2).

With a simple and fast synthesis of 3-amino-1,2,4-triazoles **3** in hand, it appeared interesting to use these compounds as precursors to prepare 7-amino-1,2,4-triazolopyrimidines **6**. Although the synthetic methods of triazolopyrimidines are well documented, the methods for the synthesis of 7-amino-1,2,4-triazolopyrimidines **6** are limited.

Indeed, 7-amino-1,2,4-triazolopyrimidines **6**[11] are easily obtained, in good yields, by simple refluxing 3-amino-1,2,4-triazoles **3** in toluene for 48 hours (Scheme 3, Table 2).

The structure of these triazolopyrimidines **6** is confirmed by ^{1}H and ^{13}C NMR and by mass spectrometry.

In this Letter, we also report a convenient method for the synthesis of new benzimidazoles **7** and imidazoles **8**.

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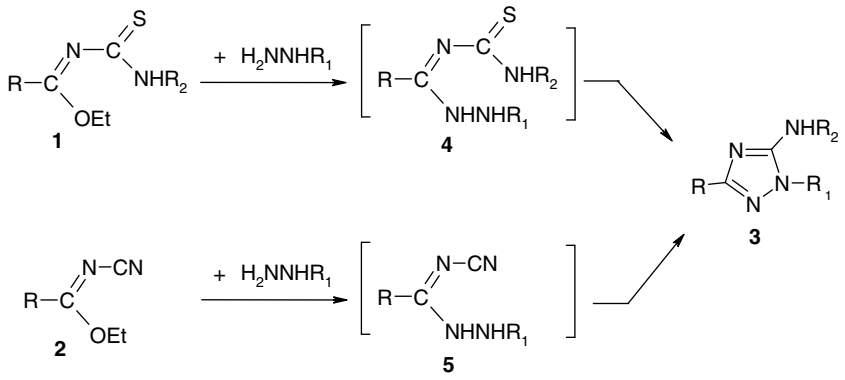
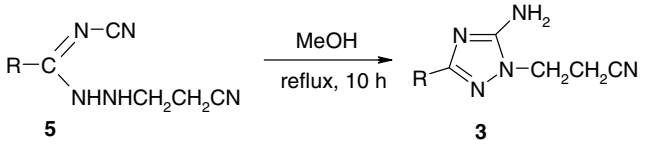


Scheme 1. Mechanism of the formation of 1,2,4-triazoles **3**.

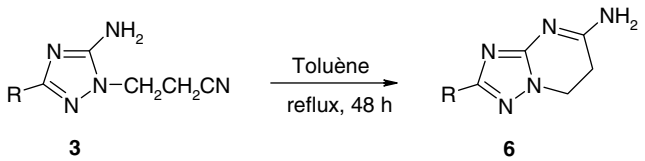
Table 1
Prepared 3-amino-1,2,4-triazoles **3**

Substrate	R	R_2	R_1	Conditions (°C, h)	Product (Yield[a] (%), mp (°C))
1a	C_6H_5	C_6H_5	H	25, 20	**3a** (70, 253)
1b	4-MeC_6H_4	C_6H_5	H	25, 20	**3b** (67, 132)
1c	C_6H_5	C_6H_5	CH_3	25, 20	**3c** (62, 265)
1d	4-MeC_6H_4	C_6H_5	CH_3	25, 20	**3d** (58, 185)
1e	C_6H_5	C_6H_5	C_6H_5	25, 20	**3e** (90, 88)
1f	4-MeC_6H_4	C_6H_5	C_6H_5	25, 20	**3f** (67, 146)
1g	$C_6H_5CH_2$	C_6H_5	H	25, 20	**3g** (72, 112)
1h	$C_6H_5CH_2$	C_6H_5	CH_3	25, 20	**3h** (65, 80)
1i	$C_6H_5CH_2$	C_6H_5	C_6H_5	25, 20	**3i** (69, 176)
1j	C_6H_5	C_6H_5	CH_2CH_2CN	25, 24	**3j** (79, 80)
1k	4-MeC_6H_4	C_6H_5	CH_2CH_2CN	25, 24	**3k** (67, 145)
1l	$C_6H_5CH_2$	C_6H_5	CH_2CH_2CN	25, 24	**3l** (67, 180)
2a	CH_3	H	CH_2CH_2CN	Reflux, 20	**3n** (86, 88)
2b	Et	H	CH_2CH_2CN	Reflux, 20	**3o** (71, 135)
2c	C_6H_5	H	CH_2CH_2CN	Reflux, 20	**3p** (68, 142)

[a] Yields of isolated, purified products. The solid compounds can be recrystallised from CCl_4.



Scheme 2. Synthesis of 1,2,4-triazoles **3**.



Scheme 3. Synthesis of 7-amino-1,2,4-triazolopyrimidines **6**.

Table 2
Preparation of 7-amino-1,2,4-triazolopyrimidines **6**

Product	R	Yield[a] (%)	Mp (°C)
6a	CH_3	64	224
6b	C_2H_5	72	235
6c	C_6H_5	70	220

[a] Yields obtained after recrystallisation from chloroform.

Indeed, imidates **1** and **2** possess several reagent sites in particular in position 1,3. They can behave, in intermolecular condensation with nucleophilic reagents, either as 1,3-difunctional agents (ß-ketoesters, ketonitriles) or as an imidic source such as orthoesters, carbon disulfide and aldehydes.

These conditions led us to imagine that the reaction of these imidates with *o*-phenylenediamine derivatives or ethylenediamine could constitute a new access to benzimidazoles and imidazoles respectively.

Effectively, good yields of benzimidazoles **7**[12] have been obtained by the reaction of *o*-phenylenediamine with imidates **2** in refluxing methanol (Scheme 4, Table 3).

Benzimidazoles **7** were characterised by their spectroscopic data of NMR and by satisfactory HRMS.

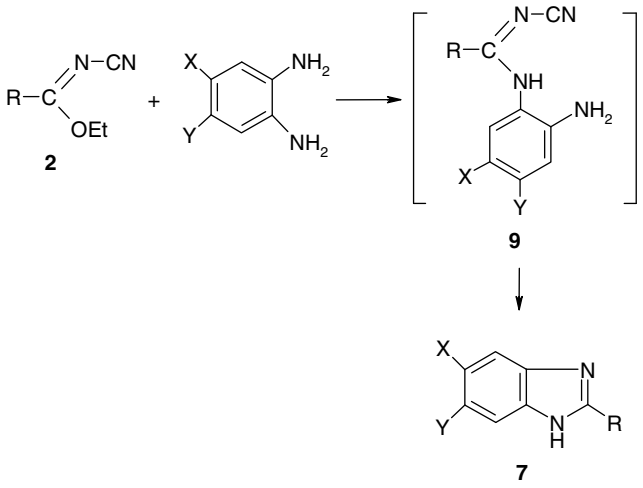
The reaction proceeds by the substitution of the ethoxy group of **2** with the *o*-phenylenediamine, which leads the unstable amidrazones **9**. Then, elimination of the cyanamide molecule yields benzimidazoles **7**.

We could not, unfortunately, obtain benzodiazepines **10** (Scheme 5). This shows that imidates **2** behave as 1,1-bis electrophilic agents towards *o*-phenylenediamine.

Our route to imidazoles **8** is shown in Scheme 6, a key intermediate being amidrazones **11**.[13]

The typical experimental procedure is outlined in Ref. 14. The yields of these reactions are collected in Table 3.

In conclusion, we have described a new convenient one-step synthesis of a new series of 3-amino triazoles and 7-amino triazolopyrimidines. The easy removal of the benzimidazoles and imidazoles makes this method competitive with other procedures. Further studies of these reactions are under investigation.

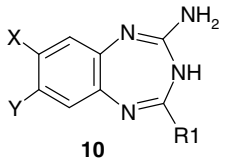


Scheme 4. Synthesis of benzimidazoles **7**.

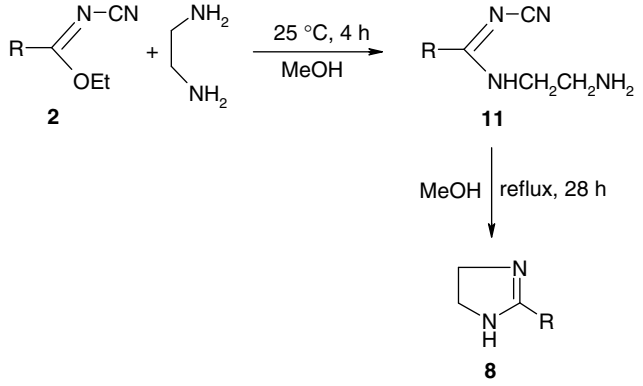
Table 3
Prepared benzimidazoles **7**, amidrazoles **11** and imidazoles **8**

Product	R	X	Y	Yield[a] (%)	Mp (°C)
7a	CH_3	H	H	79	171 (lit.[15] 170)
7b	C_6H_5	H	H	68	291 (lit.[15] 291)
7c	CH_3	CH_3	CH_3	69	251
7d	C_6H_5	CH_3	CH_3	65	221
8a	CH_3	—	—	75	267
8b	C_6H_5	—	—	69	183
11a	CH_3	—	—	78	199
11b	C_6H_5	—	—	65	181

[a] Yields of isolated, purified products. The solid compounds can be recrystallised from me.



Scheme 5. Benzotriazepines **10**.



Scheme 6. Synthesis of amidrazones **11** and imidazoles **8**.

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7. *Imidates* **1**: To a solution of iminoester (10 mmol), prepared according to the method described by Pinner,[16] in ethanol and nitrile (15/15 mL) was bubbled by dry HCl. Then, the iminoester was free of its salt, in 50 mL of ether, by a solution of sodium carbonate. Phenylthioisocyanate (10 mmol) was added dropwise at 0 °C in the thus formed iminoester. The mixture was stirred for 2 h and the ether was evaporated. The imidate **1** was recrystallised from petroleum ether.
For example, **1** (R = C_6H_5, R_2 = C_6H_5), Yield = 80%, mp = 113 °C; IR ($CHCl_3$): ν 1120, 1655, 3395 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 9.95 (m, 1H, NH), 7.10–8.0 (m, 10H, Ar), 4.35 (q, 2H, CH_2), 1.35 (t, 3H, CH_3).
Compound **1** (R = 4-MeC_6H_4, R_2 = C_6H_5), Yield = 77%, mp = 135 °C; IR ($CHCl_3$): ν 1120, 1655, 3395 cm^{-1}.^1H NMR ($CDCl_3$) δ ppm: 9.60 (m, 1H, NH), 7.00–7.50 (m, 9H, Ar), 4.30 (q, 2H, CH_2), 1.32 (t, 3H, CH_3), 2.30 (s, 3H, CH_3). *Imidates* **2**: A mixture of orthoester (0.12 mol), cyanamide (0.1 mol) and few drops of acetic acid was refluxed during 6 h and distilled then under vacuum (14 mmHg).
For example, **2** (R = CH_3), Yield = 78%, Eb = 110 °C; IR ($CHCl_3$): ν 1655, 2220 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 4.01 (q, 2H, CH_2), 2.02 (s, 3H, CH_3), 1.25 (t, 3H, CH_3).Compound **2** (R = C_2H_5), Yield = 84%, Eb = 120 °C; IR ($CHCl_3$): ν 1655, 2220 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 4.05 (q, 2H, CH_2), 1.95 (q, 2H, CH_2), 1.25 (t, 3H, CH_3), 1.20 (t, 3H, CH_3).
8. To a solution of imidates **1** or **2** (10 mmol) in methanol (40 mL) were added hydrazine derivatives (10 mmol). The solution was refluxed for 2 h and concentrated under reduced pressure to afford 3-amino-1,2,4-triazoles **3**.
For example, **3b**, IR ($CHCl_3$): ν 1540, 3435 cm^{-1}. ^1H NMR (DMSO-d_6) δ ppm: 7.0–7.60 (m, 9H, Ar), 6.33 (s, 1H, NH), 3.67 (s, 1H, NH), 2.30 (s, 3H, CH_3). Anal. Calcd: C, 72.00; N, 22.40; H, 5.60. Found: C, 71.58; N, 22.51; H, 5.61.
Compound **3h**, IR ($CHCl_3$): ν 1560, 3440 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 7.10–7.50 (m, 10H, Ar), 6.45 (s, 1H, NH), 3.93 (s, 2H, CH_2), 3.50 (s, 3H, CH_3). Anal. Calcd: C, 72.00; N, 22.40; H, 5.60. Found: C, 71.58; N, 22.51; H, 5.61.
Compound **3o**, IR ($CHCl_3$): ν 1580, 2240, 3310, 3400 cm^{-1}. ^1H NMR (DMSO-d_6) δ ppm: 4.65 (s, 2H, NH_2), 4.27 (t, 2H, CH_2), 2.85 (t, 2H, CH_2), 2.52 (q, 2H, CH_2), 1.23 (t, 3H, CH_3). Anal. Calcd: C, 72.00; N, 22.40; H, 5.60. Found: C, 71.58; N, 22.51; H, 5.61.
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10. A mixture of imidate **2** (10 mmol), 2-cyano ethylhydrazine (10 mmol) and methanol (40 mL) was stirred during one day at 25 °C. After evaporation of the solvent under reduced pressure, the precipitated product **5** was recrystallised from methanol.
For example, **5** (R = C_6H_5), Yield = 69%, mp = 104 °C; IR ($CHCl_3$): ν 2142, 2223, 3320, 3380 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 9.95 (m, 1H, NH), 6.90–7.40 (m, 5H, Ar), 4.66 (s, 1H, NH), 2.43 (s, 1H, NH), 3.96 (t, 2H, CH_2), 2.73 (t, 2H, CH_2).
11. A mixture of imidate **2** (10 mmol), 2-cyano ethylhydrazine (10 mmol) and toluene (40 mL) was stirred efficiently under reflux for 48 h. The solution was concentrated under reduced pressure to afford triazolopyrimidines **6**.
For example, **6a**, IR ($CHCl_3$): ν 1600, 3200, 3480 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 4.70 (s, 2H, NH_2), 4.20 (t, 2H, CH_2), 3.90 (t, 2H, CH_2), 2.20 (s, 3H, CH_3). ^{13}C NMR: 18.4 (s, CH_3), 159.0 (s, CH_3C=N), 152.6 (s, C=N), 39.4 (t, ^1J = 124.1 Hz, NCH_2), 31.4 (t, ^1J = 124.3 Hz, CH_2C=N), 163.2 (s, C–NH_2). HMRS calcd for $C_6H_9N_5$ ($M^{+\cdot}$): 151.085; found, 151.087.
Compound **6b**, IR ($CHCl_3$): ν 1610, 3200, 3480 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 4.80 (s, 2H, NH_2), 4.20 (t, 2H, CH_2), 3.90 (t, 2H, CH_2), 1.90 (q, 2H, CH_2), 1.20 (t, 3H, CH_3). HMRS calcd for $C_7H_{11}N_5$ ($M^{+\cdot}$): 165.101; found, 165.103.
12. To a solution of *o*-phenylenediamine (10 mmol) in methanol (40 mL) was added a solution of imidate **2** (10 mmol). The solution was then stirred under reflux for 10 h and concentrated under reduced pressure to afford benzimidazoles **7**.
For example, **7a**, IR (KBr): ν 1620, 3100, 3220 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 7.01–7.50 (m, 4H, Ar), 6.66 (s, 1H, NH), 2.51 (s, 3H, CH_3). ^{13}C NMR: 19.1 (s, CH_3); 153.1 (s, CCH_3); 115.2 123.0, 123.2, 138.2, 193.1 (Ar-ring C). HMRS calcd for $C_8H_8N_2$ ($M^{+\cdot}$): 132.068; found, 132.070.
Compound **7c**, IR (KBr): ν 1605, 3100, 3300 cm^{-1}. ^1H NMR ($CDCl_3$) δ ppm: 6.40–7.23 (s, 2H, Ar), 5.70 (s, 1H, NH), 2.30 (s, 3H, CH_3), 2.20 (s, 3H, CH_3). HMRS calcd for $C_{10}H_{12}N_2$ ($M^{+\cdot}$): 160.100; found, 160.097.

13. To a solution of ethylenediamine (10 mmol) in methanol (40 mL) was added a solution of imidate **2** (10 mmol). The solution was then stirred at room temperature for 4 h and concentrated under reduced pressure to afford amidrazones **11**.
For example, **11a**, IR (KBr): ν 1550, 2160, 3100, 3400 cm^{-1}. ^1H NMR (DMSO-d_6) δ ppm: 4.40 (s, 1H, NH), 2.80 (t, 2H, CH_2), 2.0 (t, 2H, CH_2), 2.20 (s, 3H, CH_3) 1.70 (s, 2H, NH_2).
14. To a solution of ethylenediamine (10 mmol) in methanol (40 mL) was added a solution of imidate **2** (10 mmol). The solution was then stirred under reflux for 28 h and concentrated under reduced pressure to afford imidazoles **8**.
Compound **8a**, IR (KBr): ν 1550, 3100, 3400 cm^{-1}. ^1H NMR (DMSO-d_6) δ ppm: 2.01 (s, 3H, CH_3), 3.80 (m, 4H, 2 CH_2), 4.20 (s, 1H, NH). HMRS calcd for $C_4H_8N_2$ ($M^{+\cdot}$): 84.280; found, 84.277.
Compound **8b**, IR (KBr): ν 1510, 1550, 3200–3400 cm^{-1}. ^1H NMR (DMSO-d_6) δ ppm: 6.70–7.20 (m, 5H, Ar), 3.90 (m, 4H, 2 CH_2), 5.70 (s, 1H, NH). HMRS calcd for $C_9H_{10}N_2$ ($M^{+\cdot}$): 146.084; found, 146.080.
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