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An efficient unprecedented synthesis of novel functionalized imidazoles from secondary amino-*N*-carbothioic acid (phenyl-*p*-tolylimino-methyl)amides and dimethyl acetylenedicarboxylate

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Abstract—The synthesis of functionalized imidazoles in a single-pot from the reactions of secondary amino-*N*-carbothioic acid (phenyl-*p*-tolylimino-methyl)amides with dimethyl acetylenedicarboxylate is reported. A plausible mechanistic pathway for the formation of the imidazoles is proposed.

Imidazoles are common components of a large number of natural products and pharmacologically active molecules.[1] The prevalence and prominence of this moiety makes a method, which expedites their preparation highly valuable. Despite synthetic interest in these heterocycles over the past century, few methods have emerged for the synthesis of highly functionalized imidazoles.[2] In addition, many of the methods utilize intermediates, which are difficult to prepare such as α-functionalized carbonyl, α-diamino compounds[2] or α-functionalized oxiranes[3] and most of the examples published to date for the synthesis of imidazoles are devoid of any additional functionality. Such poorly represented functionalized imidazoles having masked amine and carbomethoxy functionalities are nevertheless potential heterocyclic precursors for the synthesis of purine analogues,[4–6] or insecticides.[7] More recently, the Diels–Alder reaction of imidazoles with 1,2,4,5-tetrazines to prepare the cytotoxic marine natural product zarzissine[8] has been published.

It has been observed that simple modifications of fragments linked to thiocarbonyl groups result in the creation of new reactive centers leading to diverse functionalization possibilities[9]. Reactions of acetylenic esters with carbothioic acid amides, popularly known as thioamides, have been shown to generate various heterocyclic compounds such as thiazolidinones,[10] thiazolinones,[11] thiazonones,[10,12] thiazolotriazinediones,[2b,13] thiazines[14] and so on. Recently, Nakano et al. reported reactions of thioamides with 2 and 5 equiv of dimethyl acetylenedicarboxylate leading to the formation of pyrrole and thiophene derivatives, respectively.[15] Pradere et al. reported the cyclocondensation reaction of *N*′-(thioacyl)formamidines with dimethyl acetylenedicarboxylate leading, via sequential cycloaddition–cycloreversion–cycloaddition reactions, specifically to functionalized 4,5-dihydro-6*H*-1,3-thiazines and 6*H*-1,3-thiazines.[14] Nevertheless, there is no precedent for imidazole derivative formation. As part of our continuing interest in the synthesis of biologically important heterocycles,[16] this present letter describes a single-pot synthesis of functionalized imidazole derivatives by the reaction of thioamides **1** with dimethyl acetylenedicarboxylate.

A solution of thioamides **1** (1 mmol) and dimethyl acetylenedicarboxylate (1.2 mmol) in dry dichloromethane was stirred for 2–3 h. The reaction mixture was purified by silica gel column chromatography to give imidazole derivatives **2** (Scheme 1). The products isolated were characterized as imidazoles on the basis of analytical data and spectral evidence.[17]

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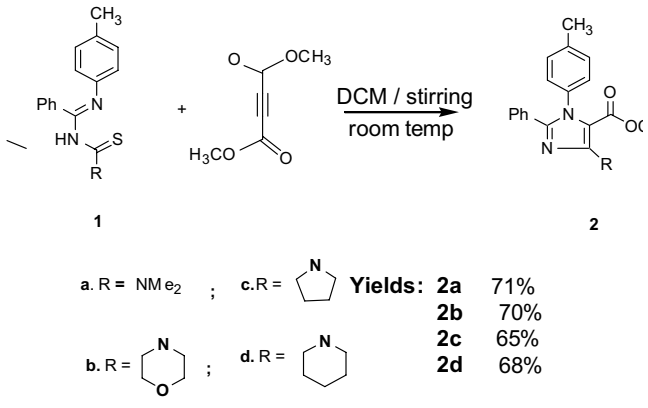


Scheme 1.

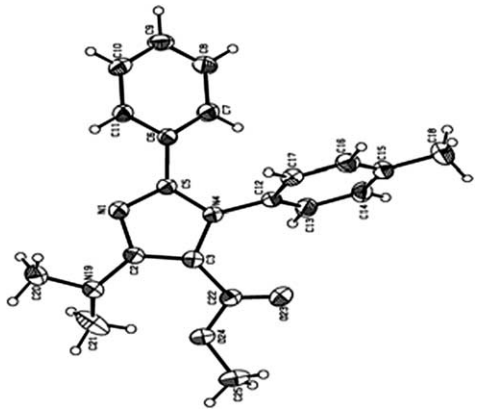
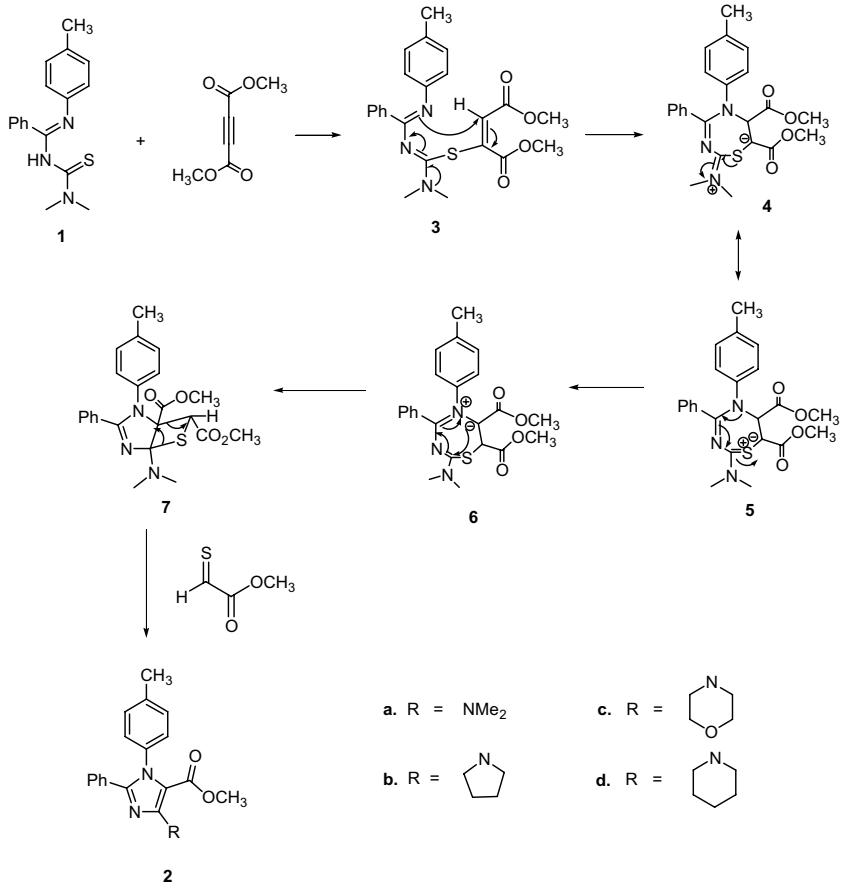


Figure 1. ORTEP representation of **2a**.

The ^{1}H NMR spectra of the products showed the absence of one of the methoxy groups and the presence of a secondary amine moiety. Their elemental analysis did not show the presence of sulfur. The ^{1}H NMR spectrum of compound **2a**, for example, exhibited singlets at δ 3.08 (6H) and 3.63 (3H) corresponding to the –NMe_2 and the –OMe protons, respectively, and a multiplet for the aromatic protons at δ 7.06–7.35 (9H). The signals for the NMe_2 and carbonyl carbons appeared at δ 42.7 and 160.3 ppm, respectively. The IR spectrum showed a carbonyl absorption at 1680 cm^{-1} whilst the mass spectrum exhibited a molecular ion peak [M^+] at m/z = 335 for $C_{20}H_{21}O_2N_3$. The assigned structure was unambiguously established with the help of X-ray crystallographic studies[18] (Fig. 1).

A plausible mechanism underlying the formation of the imidazole derivatives is shown in Scheme 2 and is thought to involve the intermediacy of cyclic azomethine ylide **6**. Sulfur being a strong nucleophile attacks one of the acetylenic carbons of dimethyl acetylenedicarboxylate to give a 1:1 adduct, which undergoes N–H proton migration to generate **3**. Intramolecular cyclization then gives thiocarbonyl ylide **4** ≡ **5**. The ylide **5** is then con-



Scheme 2.

verted to the thermodynamically stable azomethine ylide **6** as proposed by Nakano et al. in the reactions of thioamides with dimethyl acetylenedicarboxylate.[15] Intramolecular cyclization of **6** affords a bicyclic intermediate **7**, which after elimination of a thioaldehyde molecule finally yields imidazoles **2**.

In conclusion, the reactions of thioamides **1** with dimethyl acetylenedicarboxylate result in a single-pot and exclusive synthesis of novel imidazole derivatives via a cyclic azomethine ylide intermediate. The method reported herein assumes significance because of the regiospecific introduction of latent amine and carbomethoxy (–CO_2Me) groups, which are amenable to further elaboration through N–C and N-heteroatom bond formation and hence lead to concise syntheses of purine analogues. Further studies on the scope and limitations of these reactions are in progress.

References and notes

1. For examples, see: (a) Greenlee, W. J.; Siegl, P. K. S. *Ann. Rep. Med. Chem.* **1992**, *27*, 59; (b) Hodges, J. C.; Hamby, J. M.; Blankley, C. J. *Future Drugs* **1992**, *17*, 575; (c) Shilcrat, S. C.; Mokhallalati, M. K.; Fortunak, J. M. D.; Pridgen, L. N. *J. Org. Chem.* **1997**, *62*, 8449; (d) Meanwell, N. A.; Romine, J. L.; Seiler, S. M. *Future Drugs* **1994**, *19*, 361; (e) Rizzi, J. P.; Nagel, A. A.; Rosen, T.; McLean, S.; Seeger, T. *J. Med. Chem.* **1990**, *33*, 2721; (f) Shapiro, G.; Gomez-Lor, B. *J. Org. Chem.* **1994**, *59*, 5524; (g) Adams, J. L.; Boehm, J. C.; Kassis, S.; Goycki, P. D.; Webb, E. F.; Hall, R.; Sorenson, M.; Lee, J. C.; Ayrton, A.; Griswold, D. E.; Gallagher, T. F. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3111.
2. For imidazole synthesis, see: (a) Ebel, K. In *Methoden der Organischen Chemie* (Houben-Weyl); Band E8c, HetareneIII/Teil 3; Schaumann, E., Ed.; George Thieme: Stuttgart, 1994; pp 1–215; (b) Lantos, I.; Zhang, W. Y.; Shui, X.; Eggleston, D. S. *J. Org. Chem.* **1993**, *58*, 7092; (c) Nunami, K.; Yamada, M.; Fukui, T.; Matsumoto, K. *J. Org. Chem.* **1994**, *59*, 7635.
3. Guillemet, M.; Robert, A.; Baudy-Floc'h, M. *Tetrahedron Lett.* **1995**, *36*, 547, and references cited therein.
4. (a) Murakami, T.; Otsuka, M.; Kobayashi, S.; Ohno, M. *Heterocycles* **1981**, *16*, 1315; (b) Neilson, F. E.; Pedersen, E. B. *Tetrahedron* **1982**, *38*, 1435; (c) Dias, A. M.; Cabral, I. M.; Proenca, M. F.; Booth, B. L. *J. Org. Chem.* **2002**, *67*, 5546, and references cited therein.
5. (a) Xu, Y.-Z.; Yakushijin, K.; Horne, D. A. *Tetrahedron Lett.* **1993**, *34*, 6981; (b) Xu, Y.-Z.; Yakushijin, K.; Horne, D. A. *J. Org. Chem.* **1996**, *61*, 9569; (c) Braun, M.; Buchi, G.; Bushey, D. F. *J. Am. Chem. Soc.* **1978**, *100*, 4208.
6. Dang, Q.; Liu, Y.; Erion, M. D. *J. Am. Chem. Soc.* **1999**, *121*, 5833.
7. Hoffman, H.; Hamman, I.; Homeyer, B. Ger. Offen. No 2431848, 1976; *Chem. Abstr*. **1976**, *84*, 121838x.
8. Wan, Z.-K.; Woo, G. H. C.; Snyder, J. K. *Tetrahedron* **2001**, *57*, 5497.
9. Jagodzinski, T. S. *Chem. Rev.* **2003**, *103*, 197, and references cited therein.
10. (a) Acheson, R. M.; Wallis, S. D. *J. Chem. Soc., Perkin Trans. 1* **1981**, 415; (b) Berseneva, V. S.; Tkachev, A. V.; Morzherin, Y. Y.; Dehaen, W.; Bakulev, V. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2133; (c) Kauss, V. Y.; Liepinsh, E. E.; Kalvinsh, I. Y. *Khim. Geterotsikl. Soedin* **1990**, 120.
11. Coen, S.; Ragonnet, B.; Viellescazes, C. *Heterocycles* **1985**, *23*, 1225.
12. (a) Giannola, L. I.; Palazzo, S.; Agozzino, P.; Lamartina, L. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1428; (b) Giammona, G.; Neri, M.; Carlisi, B.; Palazzo, A.; Rosa, C. L. *J. Heterocycl. Chem.* **1991**, *28*, 325.
13. (a) Giannola, L. I.; Giammona, G.; Palazzo, S.; Lamartina, L. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2707; (b) Bakulev, V. A.; Berseneva, V. S.; Belskaia, N. P.; Morzherin, Y. Y.; Zaitsev, A.; Dehaen, W.; Luyten, I.; Toppet, S. *Org. Biomol. Chem.* **2003**, *1*, 134.
14. Gokou, C. T.; Pradere, J. P.; Quiniou, H. *J. Org. Chem.* **1985**, *50*, 1545.
15. Nakano, H.; Ishibashi, T.; Sawada, T. *Tetrahedron Lett.* **2003**, *44*, 4175.
16. (a) Mazumdar, S. N.; Mahajan, M. P. *Synthesis* **1990**, *5*, 417; (b) Dey, P. D.; Sharma, A. K.; Rai, S. N.; Mahajan, M. P. *Tetrahedron Lett.* **1995**, *57*, 7459; (c) Mazumdar, S. N.; Sharma, M.; Mahajan, M. P. *Tetrahedron Lett.* **1986**, *27*, 5875; (d) Mazumdar, S. N.; Sharma, M.; Mahajan, M. P. *Tetrahedron Lett.* **1987**, *28*, 2641; (e) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron Report No. 595*, **2002**, *58*, 379.
17. (a) *5-Dimethylamino-2-phenyl-3-p-tolyl-3H-imidazoIe-4-carboxylic acid methyl ester* (**2a**): mp 139–140 °C. Yield: 71%; IR(KBr) ν_{max}: 1689 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, Me_4Si): δ 2.38 (s, 3H, –CH_3), 3.08 (s, 6H, –$N(CH_3)_2$), 3.63 (s, 3H, –OCH_3), 7.06–7.35 (m, 9H, arom); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si): δ 21.2 (–CH_3), 42.7 (–$N(CH_3)_2$), 50.7 (–OCH_3), 108.7, 127.8, 127.9, 128.7, 128.9, 129.2, 129.9, 135.6, 138.2, 148.1, 158.6 (–C=N), 160.3 (–C=O); MS: *m/z*: 335. Anal. Calcd for $C_{20}H_{21}O_2N_3$: C, 71.64; H, 6.27; N, 12.54. Found: C, 71.59; H, 6.30; N, 12.61; (b) *5-Morpholin-4-yl-2-phenyl-3-p-tolyl-3H-imidazole-4-carboxylic acid methyl ester* (**2b**): mp 142–143 °C. Yield: 70%; IR (KBr) ν_{max}: 1689 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, Me_4Si): δ 2.41 (s, 3H, –CH_3); 3.48 (m, 4H, –CH_2–N–CH_2–); 3.60 (s, 3H, –OCH_3); 3.89 (m, 4H, –CH_2–O–CH_2–); 7.05–7.33 (m, 9H, arom); ^{13}C NMR (200 MHz, $CDCl_3$, Me_4Si): δ 21.3 (–CH_3), 45.4 (–CH_2–N–CH_2), 50.9 (–OCH_3), 67.1 (–CH_2–O–CH_2), 110.2, 127.7, 128.0, 128.9, 129.0, 129.4, 129.7, 135.5, 138.5, 147.9, 157.7 (–C=N), 160.0 (–C=O); MS: *m/z*: 377. Anal. Calcd for $C_{22}H_{23}O_3N_3$: C, 70.03; H, 6.10; N, 11.14. Found: C, 69.90; H, 6.27; N, 11.20.
18. *Crystal data and structure refinement for* **2a**: CCDC reference: CCDC 235730; empirical formula: $C_{20}H_{21}N_3O_2$; formula weight: 335.40; temperature: 293(2) K; wavelength: 0.71073 Å; crystal system: monoclinic; spacegroup: $P2_1$; unit cell dimensions: a = 5.9295(6) Å, a = 90°, b = 10.0750(10) Å, b = 92.603(2)°, c = 14.9191(15) Å, g = 90°; volume: 890.34(15) $Å^3$; Z: 2; density (calculated): 1.251 g/m^3; absorption coefficient: 0.082 mm^{-1}; F(000): 356; θ range for data collection: 2.44–28.03°; index ranges: $-7 \leqslant h < 7$, $-13 \leqslant k \leqslant 13$, $-19 \leqslant 1 \leqslant 17$; reflections collected: 5480; independent reflections: 3626[R(int) = 0.0164]; completeness to θ: 28.03°, 95.6%.
Refinement method: full-matrix least-squares on F^2; data/restraints/parameters: 3626/1/230; goodness-of-fit on F^2: 1.031; final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0482, $wR2$ = 0.1183; R indices (all data): $R1$ = 0.0565, $wR2$ = 0.1245; absolute structure parameter: 2.0(17); largest diff. peak and hole: 0.170 and −0.205 e $Å^{-3}$.