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Green synthesis of imidazole derivatives using *N*-formylmorpholine as green solvent

Narges Ghasemi*

National Petrochemical Company (NPC), petrochemical Research and Technology Company, Arak Center, Iran

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Abstract: An efficient synthesis of functionalized imidazoles via a one-pot reaction between ninhydrin, primary alkylamines, arylisothiocyanates, acetylenic esters and N-formylmorpholine as green solvent is described.

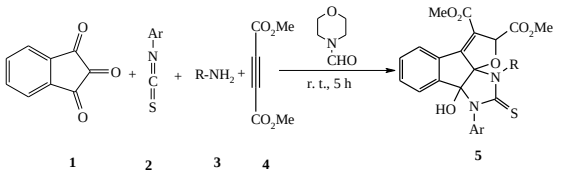
Keywords: Ninhydrin, Primary amine, Arylisothiocyanates, Dialkyl acetylenedicarboxylates, Multi component reaction.

Introduction

Tandem reactions (TRs) are of paramount importance in the context of green chemistry as they offer a convenient strategy for the rapid, elegant and convergent construction of complex organic molecules without isolating and purifying the intermediates, resulting in substantial minimization of waste, labor, time and cost [1-6]. Tandem processes lead to skeletal changes rather than merely functional group transformations. Therefore, TRs have become an increasingly active area of research, yielding novel chemical scaffolds for drug discovery efforts. Also, multi-component reactions (MCRs) have been generally used by synthetic chemists as a simplistic means to create molecular diversity from bifunctional substrates that react successively in an intramolecular way. Devising such types of MCRs that achieve the formation of multiple bonds in a single operation is one of the major challenges in modern organic synthesis. As such processes avoid time-consuming and costly purification processes, as well as protection–deprotection steps; they are inherently more environmentally benign and atom-economic.

They provide a powerful tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocyclic [7-10]. Also, imidazoles play a prominent role in Nature and exist in many natural products [11-14]. The imidazole system can be found in numerous medically relevant compounds such as the fungicide Ketoconazole [15] and its family members, the benzodiazepine antagonist Flumazenil [16]. Also, imidazoles play a prominent role in Nature and exist in many natural products [11-14]. The imidazole system can be found in numerous medically relevant compounds such as the fungicide Ketoconazole [15] and its family members, the benzodiazepine antagonist Flumazenil [16]. Hence, we report an efficient tandem reaction between ninhydrin **1**, arylisothiocyanates **2**, primary alkylamines **3**, and dimethyl acetylenedicarboxylate (DMAD, **4**) at r.t. in N-formylmorpholine as green solvent, which constitutes a direct synthesis of imidazoles **5** in good yields (Scheme **1**).

*Corresponding author: Tel: 0098-8633677201-9; Fax: 0098-8633677203, E-mail: naghasemi.16@gmail.com



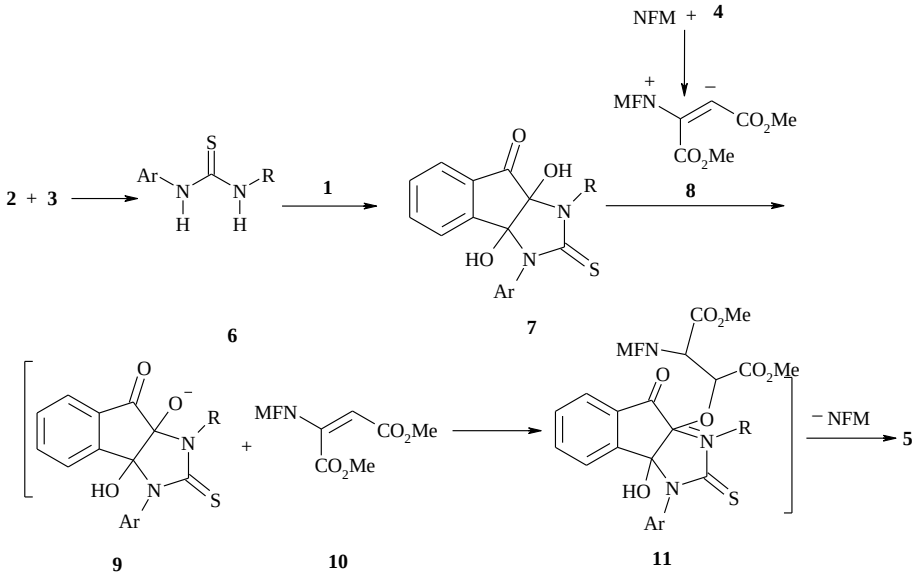
2, 3, 5	Ar	R	Yield (%) of 5
a	ph	4-MeO-Bn	80
b	4-F-C_6H_4	4-MeO-Bn	75
c	2,4-Cl-C_6H_4	4-MeO-Bn	80
d	4-NO_2-C_6H_4	4-MeO-Bn	78
e	4-NO_2-C_6H_4	4-Me-Bn	74
f	4-F-C_6H_4	4-Me-Bn	76

Scheme 1: Synthesis of imidazole derivatives in NFM.

Results and discussion

An efficient tandem reaction is performed between ninhydrin **1**, isothiocyanates **2**, primary alkylamines **3**, and dimethyl acetylenedicarboxylate **4** at r.t. in NFM as green solvent, which constitutes a direct synthesis of imidazoles **5** in good yields (Scheme **1**).

The structures of compounds **5** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. For example, the ^{1}H NMR spectrum of **5a** exhibited five sharp singlets for methoxy (3.67, 3.77, and 3.83 ppm), hydroxyl (4.70 ppm), and methine (5.65 ppm) protons, along with characteristic multipletes for the aromatic protons (6.80-7.51 ppm). The benzylic methylene protons are diastereotopic and show an AX system at 4.90 and 5.10 ppm (^3J = 15.0 Hz). The ^{13}C NMR spectrum of **5a** exhibited 28 distinct resonances which further confirmed the proposed structure. The IR spectrum of **5a** displayed characteristic carbonyl bands. The mass spectra of **5a** exhibited the molecular ion peak at the appropriate *m*/*z* = 542. The ^{1}H NMR and ^{13}C NMR spectra of **5b**-**5f** were similar to those for **5a** except for the imidazole moieties, which exhibited characteristic resonances in appropriate regions of the spectrum. Although the mechanistic aspects of the reaction are not known, a reasonable explanation may be proceeded to explicate the product formation. Presumably, the reaction starts with formation of the urea derivative **6**, followed by its regioselective addition to ninhydrin (**1**) to generate **7**. This intermediate protonates the zwitterionic species **8** formed from NFM and DMAD. Then, the positively charged ion **10** is attacked by the conjugate base of the OH-acidic **7** to form phosphorane **11**, which undergoes an intramolecular Wittig reaction to produce product **5**. According to this mechanism, the formation of a single product **7** from the reaction of **1** with the unsymmetrical urea derivative **6** is presumably controlled by addition of the stronger nucleophilic *N*-alkyl nitrogen atom of **7** to the central carbonyl group of **1** (Scheme **2**).



Scheme 2: Proposed mechanism for the formation of **5.**

Conclusion

In summary, we report a tandem transformation involving ninhydrin, phenylisocyanate (or phenylisothiocyanate), primary alkylamines, N-formylmorpholine, and DMAD, which affords a new route to the synthesis of imidazoles. The present procedure has the advantage that, not only is the reaction performed under neutral conditions, but also the reactants can be mixed without any prior activation or modification.

Experimental

All chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV.

IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H, and ^{13}C NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. ^{1}H, and ^{13}C, spectra were obtained for solutions in $CDCl_3$ using TMS as internal standard or 85% H_3PO_4 as external standard.

General procedure for preparation of compounds 5a-f.

A solution of the heterocumulene **2** (2 mmol) and primary alkylamine **3** (2 mmol) in 10 mL of CH_2Cl_2 was stirred for 5 min at r.t. Then, 0.32 g of ninhydrin (2 mmol) was added and the mixture was stirred for 10 min. After addition of 0.52 g of Ph_3P (2 mmol), 0.28 g of DMAD (2 mmol) was added. After completion of the reaction [3-5 h, TLC (AcOEt/hexane 1:4) monitoring], the solvent was evaporated, and the residue was purified by column chromatography (silica gel (230–400 mesh, Merck), hexane/AcOEt 5:1): pure product.

Dimethyl 10b-hydroxy-3-(4-methoxybenzyl)-2-oxo-3-phenyl-2,3,5,10b-tetrahydro-1H-furo[2',3':2,3] indeno[1,2-d]imidazole-5,6-dicarboxylate (5a):

Yield: 0.92 g (85%). Pale yellow powder. M.p. 197-200°. IR (KBr): 3352, 2918, 1715, 1510, 1413, 1336, 1256. ^{1}H NMR: 3.67 (*s*, MeO), 3.77 (*s*, MeO), 3.83 (*s*, MeO), 4.70 (*s*, OH), 4.90 (*d*, ^3J = 15.0, CH), 5.10 (*d*, ^3J = 15.0, CH), 5.65 (*s*, CH), 6.80 (*d*, ^3J = 7.4, 2 CH), 6.91 (*t*, ^3J = 7.2, CH), 7.13 (*d*, ^3J = 7.3, 2 CH), 7.26 (*t*, ^3J = 7.2, 2 CH), 7.27 (*d*, ^3J = 7.3, 2 CH), 7.31 (*t*, ^3J = 7.2, CH), 7.33 (*d*, ^3J = 7.3, 2 CH), 7.51 (*t*, ^3J = 7.2, CH). ^{13}C NMR: 47.6 (CH_2N), 52.9 (MeO), 53.0 (MeO), 53.8 (MeO), 88.8 (CH), 114.3 (C), 114.6 (C), 123.2 (2 CH), 124.6 (CH), 125.1 (CH), 126.1 (CH), 126.5 (CH), 126.8 (CH), 127.0 (CH), 128.7 (C), 128.9 (2 CH), 129.0 (CH), 129.1 (CH), 129.3 (CH), 131.8 (C), 133.5 (C), 136.5 (C), 143.9 (C), 145.0 (C), 158.9 (C), 159.5 (C=O), 167.2 (C=O), 170.6 (C=O). EI-MS: 542 (5) [M^+], 403 (15), 372 (44), 288 (32), 133 (35), 121 (100), 77 (40), 57 (30). Anal. Calc. for $C_{30}H_{26}N_2O_8$ (542.54): C 66.42, H 4.83, N 5.16, found: C 66.69, H 4.88, N 5.20.

Dimethyl 1-(4-fluorophenyl)-10b-hydroxy-3-(4-methoxybenzyl)-2-thioxo-2,3,5,10b-tetrahydro-1H-furo[2',3':2,3]indeno[1,2-d]imidazole-5,6-dicarboxylate **(5b):**

Yield: 0.86 g (75%). Pale yellow powder. M.p. 202-205°. IR (KBr): 3446, 2946, 1735, 1508, 1439, 1364, 1218. ^{1}H NMR: 3.63 (*s*, MeO), 3.74 (*s*, MeO), 3.80 (*s*, MeO), 4.77 (*s*, OH), 5.17 (*d*, ^3J = 15.0, CH), 5.26 (*d*, ^3J = 15.1, CH), 5.29 (*s*, CH), 6.78 (*d*, ^3J = 7.4, 2 CH), 6.90 (*d*, ^3J = 7.3, 2 CH), 7.12 (*d*, ^3J = 7.3, 2 CH), 7.21 (*d*, ^3J = 7.3, 2 CH),7.39 (*t*, ^3J = 7.2, CH), 7.42 (*d*, ^3J = 7.1, 2 CH), 7.49 (*t*, ^3J = 7.2, CH). ^{13}C NMR: 47.6 (CH_2N), 52.9 (MeO), 53.0 (MeO), 53.8 (MeO), 88.9 (CH), 114.3 (C), 114.6 (C), 123.2 (2 CH), 125.6 (CH), 125.9 (CH), 126.0 (CH), 127.7 (CH), 129.8 (CH), 129.9 (CH), 132.1 (C), 132.3 (2 CH), 133.1 (CH), 133.3 (CH), 133.4 (C), 133.8 (C), 135.8 (C), 139.6 (C), 147.7 (C), 150.8 (C), 159.8 (C), 164.3 (C=O), 170.7 (C=O), 182.6 (C=S). EI-MS: 576 (3) [M^+], 400 (15), 288 (44), 229 (38), 167 (45), 121 (100), 95 (85), 59 (90). Anal. Calcd for $C_{30}H_{25}FN_2O_7S$ (576.59): C 62.49, H 4.37, N 4.86, found: C 62.64, H 4.40, N 4.90.

Dimethyl 1-(2,4-dichlorophenyl)-10b-hydroxy-3-(4-methoxybenzyl)-2-thioxo-2,3,5,10b-tetrahydro-1H-furo[2',3':2,3]indeno[1,2-d]imidazole-5,6-dicarboxylate **(5c):**

Yield: 1.00 g (80%). Pale orange powder. M.p. 205-208°. IR (KBr): 3418, 2941, 1727, 1512, 1457, 1338, 1261. ^{1}H NMR: 3.71 (*s*, MeO), 3.76 (*s*, MeO), 3.81 (*s*, MeO), 4.77 (*s*, OH), 5.24 (*d*, ^3J = 15.0, CH), 5.28 (*d*, ^3J = 15.0, CH), 5.39 (*s*, CH), 6.88 (*d*, ^3J = 7.4, CH), 7.14 (*d*, ^3J = 7.1, 2 CH), 7.22 (*d*, ^3J = 7.3, CH), 7.32 (*d*, ^3J = 7.2, 2 CH), 7.35 (*t*, ^3J = 7.2, CH), 7.40 (*d*, ^3J = 7.3, 2 CH), 7.46 (*t*, ^3J = 7.2, CH), 8.07 (*s*, CH). ^{13}C NMR: 47.6 (CH_2N), 52.9 (MeO), 53.1 (MeO), 53.8 (MeO), 88.9 (CH), 114.3 (C), 114.6 (C), 123.2 (2 CH), 125.6 (CH), 125.9 (CH), 126.0 (CH), 127.7 (CH), 129.8

(CH), 129.9 (CH), 132.1 (C), 132.3 (2 CH), 133.1 (CH), 133.3 (CH), 133.4 (C), 133.8 (C), 135.8 (C), 139.6 (C), 147.7 (C), 150.8 (C), 159.8 (C), 164.3 (C=O), 170.7 (C=O), 182.6 (C=S). EI-MS: 627 (3) [M^+], 400 (15), 288 (44), 229 (38), 144 (45), 121 (100), 95 (85), 59 (90). Anal. Calcd for $C_{30}H_{24}Cl_2N_2O_7S$ (627.49): C 57.42, H 3.85, N 4.46, found: C 57.75, H 3.88, N 4.50.

Dimethyl 10b-hydroxy-3-(4-methoxybenzyl)-1-(4-nitrophenyl)-2-thioxo-2,3,5,10b-tetrahydro-1H-furo[2',3':2,3]indeno[1,2-d]imidazole-5,6-dicarboxylate (5d):

Yield: 0.94 g (78%). Pale yellow powder. M.p. 203-207°. IR (KBr): 3436, 2930, 1721, 1512, 1443, 1338, 1267. ^{1}H NMR: 3.76 (*s*, MeO), 3.78 (*s*, MeO), 3.83 (*s*, MeO), 5.16 (*s*, OH), 5.28 (*d*, ^3J = 15.0, CH), 5.31 (*d*, ^3J = 15.0, CH), 5.65 (*s*, CH), 7.15 (*d*, ^3J = 7.4, 2 CH), 7.18 (*d*, ^3J = 7.4, 2 CH), 7.19 (*d*, ^3J = 7.4, 2 CH), 7.39 (*t*, ^3J = 7.2, CH), 7.52 (*d*, ^3J = 7.3, 2 CH), 7.86 (*t*, ^3J = 7.2, CH), 8.20 (*d*, ^3J = 7.3, 2 CH). ^{13}C NMR: 47.6 (CH_2N), 53.0 (MeO), 53.1 (MeO), 53.8 (MeO), 88.9 (CH), 114.3 (C), 114.6 (C), 123.2 (2 CH), 125.6 (CH), 125.9 (CH), 126.0 (CH), 127.7 (CH), 129.8 (CH), 129.9 (CH), 132.1 (C), 132.3 (2 CH), 133.1 (CH), 133.3 (CH), 133.4 (C), 133.8 (C), 135.8 (C), 139.6 (C), 147.7 (C), 150.8 (C), 159.8 (C), 164.3 (C=O), 170.7 (C=O), 182.6 (C=S). EI-MS: 603 (3) [M^+], 400 (15), 289 (44), 229 (38), 149 (45), 121 (100), 77 (85), 57 (90). Anal. Calcd for $C_{30}H_{25}N_3O_9S$ (603.59): C 59.70, H 4.17, N 6.96, found: C 59.97, H 4.21, N 6.88.

Dimethyl 10b-hydroxy-3-(4-methylbenzyl)-1-(4-nitrophenyl)-2-thioxo-2,3,5,10b-tetrahydro-1H-furo[2',3':2,3]indeno[1,2-d]imidazole-5,6-dicarboxylate (5e):

Yield: 0.87 g (74%). Pale orange powder. M.p. 202-205°. IR (KBr): 3392, 2928, 1721, 1512, 1443, 1338, 1246. ^{1}H NMR: 2.38 (*s*, Me), 3.77 (*s*, MeO), 3.80 (*s*, MeO), 5.10 (*s*, OH), 5.28 (*d*, ^3J = 15.0, CH), 5.31(*d*, ^3J = 15.0, CH), 5.65 (*s*, CH), 6.91 (*d*, ^3J = 7.4, 2 CH), 7.11 (*d*, ^3J = 7.3, 2 CH), 7.13 (*d*, ^3J = 7.3, 2 CH), 7.26 (*t*, ^3J = 7.2, CH), 7.31 (*d*, ^3J = 7.3, 2 CH), 7.33 (*t*, ^3J = 7.2, CH), 8.01 (*d*, ^3J = 7.3, 2 CH). ^{13}C NMR: 21.0 (Me), 47.8 (CH_2N), 53.1 (MeO), 54.1 (MeO), 88.8 (CH), 113.6 (C), 114.6 (C), 123.6 (2 CH), 124.6 (CH), 125.1 (CH), 126.7 (CH), 127.7 (CH), 128.3 (CH), 129.3 (CH), 128.7 (C), 130.0 (CH), 131.2 (CH), 131.4 (2 CH), 131.8 (C), 133.5 (C), 136.5 (C), 140.9 (C), 143.9 (C), 145.0 (C), 158.9 (C), 161.5 (C=O), 170.8 (C=O), 181.8 (C=S). EI-MS: 587(3) [M^+], 400 (15), 299 (44), 229 (38), 180 (45), 122 (100), 105 (85), 59 (90). Anal. Calcd for $C_{30}H_{25}N_3O_8S$ (587.60): C 61.32, H 4.29, N 7.15, found: C 61.54, H 4.31, N 7.20.

Dimethyl 1-(4-fluorophenyl)-10b-hydroxy-3-(4-methylbenzyl)-2-thioxo-2,3,5,10b-tetrahydro-1H-furo[2',3':2,3]indeno[1,2-d]imidazole-5,6-dicarboxylate (5f):

Yield: 0.85 g (76%). Pale orange powder. M.p. 202-206°. IR (KBr) (ν_{max}/cm^{-1}): 3382, 2928, 1726, 1512, 1423, 1338, 1216. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.37 (s, Me), 3.77 (s, MeO), 3.80 (s, MeO), 5.10 (*s*, OH), 5.28 (*d*, ^3J = 15.0, CH), 5.31(*d*, ^3J = 15.0, CH), 5.65 (*s*, CH), 7.07 (*d*, ^3J = 7.4, 2 CH), 7.11 (*d*, ^3J = 7.3, 2 CH), 7.18 (*d*, ^3J = 7.3, 2 CH), 7.29 (*d*, ^3J = 7.3, 2 CH), 7.43 (*t*, ^3J = 7.2, CH), 7.52 (*d*, ^3J = 7.3, 2 CH), 7.59 (*t*, ^3J = 7.2, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 23.3 (Me), 47.8 (CH_2N), 53.1 (MeO), 54.1 (MeO), 88.8 (CH), 113.6 (C), 114.6 (C), 123.6 (2 CH), 124.6 (CH), 125.1 (CH), 126.7 (CH), 127.7 (CH), 128.3 (CH), 129.3 (CH), 128.7 (C), 130.0 (CH), 131.2 (CH), 131.4 (2 CH), 131.8 (C), 133.5 (C), 136.5 (C), 140.9 (C), 143.9 (C), 145.0 (C), 158.9 (C), 161.5 (C=O), 170.8 (C=O), 181.8 (C=S). EI-MS: 560 (3) [M^+], 442 (15), 288 (44), 272 (38), 167 (45), 105 (100), 95 (85), 59 (90). Anal. Calcd for $C_{30}H_{25}FN_2O_6S$ (560.59): C 64.28, H 4.49, N 5.00, found: C 64.66, H 4.53, N 5.10.

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