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A facile multicomponent synthesis of functionalized imidazoles

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Abstract: An efficient synthesis of functionalized tetrahydroimidazoles via a one-pot tandem reaction between ninhydrin, primary alkylamines, arylisocyanates or arylisothiocyanates, acetylenic esters and triphenylphosphine is described.

Keywords: Ninhydrin, Primary amine, Arylisocyanates, Dialkyl acetylenedicarboxylates, Multicomponent 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, imidazoles play a prominent role in nature and exist in many natural products [7-10]. The imidazole system can be found in numerous medically relevant compounds such as the fungicide Ketoconazole [11] and its family members, the benzodiazepine antagonist Flumazenil [12]. Hence, we report an efficient tandem reaction between ninhydrin **1**, arylisocyanates **2**, primary alkylamines **3**, and dimethyl acetylenedicarboxylate (DMAD, **4**) at room temperature, which constitutes a direct synthesis of functionalized tetrahydro-1*H*-furoindeno[1,2-d]imidazoles **5** in 74-85% yields (Scheme **1**).

Results and discussion

An efficient tandem reaction is performed between ninhydrin **1**, arylisocyanates **2**, primary alkylamines **3**, and dimethyl acetylenedicarboxylate (DMAD, **4**) at room temperature, which constitutes a direct synthesis of functionalized tetrahydro-1*H*-furoindeno[1,2-d]imidazoles **5** in 78-87% 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 three 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 (^{3}J = 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. 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 protonated the zwitterionic species **8** formed from Ph_3P and DMAD **4**. 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**.

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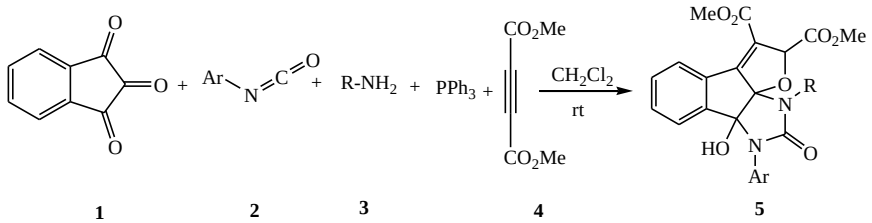
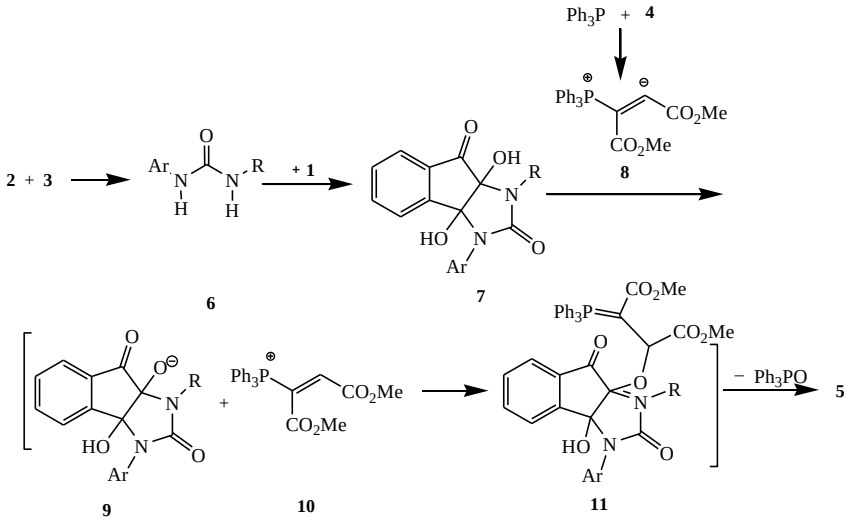
According to this mechanism, the formation of a single product **7** from the reaction of **1** with the unsymmetrical urea derivative **6** is presumably controlled by addition of the stronger nucleophilic *N*-alkyl nitrogen atom of **7** to the central carbonyl group of **1** (Scheme **2**).



1 **2** **3** **4** **5**

2, 3, 5	Ar	R	Time (min)	Yield (%) of **5**
a	Ph	4-MeO-Bn	180	85
b	Ph	4-Me-Bn	240	87
c	Ph	Allyl	260	78
d	Ph	Me	300	82
e	Ph	Et	210	80

Scheme 1: The reaction between ninhydrin, arylisocyanates, primary alkylamines, and dimethyl acetylenedicarboxylate.



6 **7** **8** **9** **10** **11**

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

Conclusion

In summary, we report a tandem transformation involving ninhydrin, phenylisocyanate, primary alkylamines, Ph_3P, and DMAD, which affords a new route to the stereoselective synthesis of functionalized 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. ^1H, and ^{13}C NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. ^1H, 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-e:

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 **1** (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) using hexane/AcOEt 5:1).

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°C. IR (KBr): 3352, 2918, 1715, 1510, 1413, 1336, 1256 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ 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) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 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) ppm. MS: *m*/*z* (%) = 542 (35) [M^+], 527 (55), 525 (43), 512 (65), 511 (90). Anal. Calcd for $C_{30}H_{26}N_2O_8$ (542.54): C 66.42, H 4.83, N 5.16; Found: C 66.31, H 4.53, N 5.12.

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

Yield: 0.92 g (87%). Pale yellow powder. M.p. 191-193°C. IR (KBr): 3302, 2948, 1701, 1516, 1433, 1328, 1226 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ 2.76 (*s*, Me), 3.79 (*s*, MeO), 3.83 (*s*, MeO), 5.10 (*s*, OH), 5.17 (*d*, ^3J = 15.0, CH), 5.28 (*d*, ^3J = 15.0, CH), 5.65 (*s*, CH), 6.81 (*d*, ^3J = 7.4, 2 CH), 7.05 (*t*, ^3J = 7.2, CH), 7.11 (*d*, ^3J = 7.3, 2 CH), 7.22 (*t*, ^3J = 7.2, 2 CH), 7.26 (*d*, ^3J = 7.3, 2 CH), 7.30 (*t*, ^3J = 7.2, CH), 7.37 (*d*, ^3J = 7.3, 2 CH), 7.61 (*t*, ^3J = 7.2, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 21.3 (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), 127.7 (2 CH), 129.3 (CH), 128.7 (C), 130.0 (2 CH), 131.2 (2 CH), 131.4 (2 CH), 131.8 (C), 134.5 (C), 136.5 (C), 143.9 (C), 145.0 (C), 158.9 (C), 159.1 (C=O), 161.5 (C=O), 170.8 (C=O) ppm. Anal. Calcd for $C_{30}H_{26}N_2O_7$ (526.54): C 68.43, H 4.98, N 5.32; Found: C 68.53, H 4.72, N 5.22.

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

Yield: 0.72 g (78%). Pale orange powder. M.p. 193-195°C. IR (KBr): 3392, 2928, 1721, 1512, 1443, 1338, 1246 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ 3.47 (*s*, MeO), 3.77 (*s*, MeO), 3.81 (*d*, CH_2N), 5.10 (*s*, OH), 5.17 (*d*, ^3J = 15.0, CH), 5.28 (*d*, ^3J = 15.0, CH), 5.76-5.83 (*m*, CH), 6.04 (*s*, CH), 6.98 (*t*, ^3J = 7.4, CH), 7.26 (*t*, ^3J = 7.2, CH), 7.31 (*d*, ^3J = 7.3, 2 CH), 7.33 (*t*, ^3J = 7.3, CH), 7.33 (*t*, ^3J = 7.2, 2 CH),7.81 (*d*, ^3J = 7.2, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 43.1 (CH_2N), 53.5 (MeO), 53.6 (MeO), 78.8 (CH), 116.1 (C), 120.8 (C), 123.6 (CH_2), 124.0 (CH), 129.6 (CH), 134.1 (2 CH), 135.8 (CH), 136.5 (C), 139.7 (CH), 142.6 (2 CH), 131.4 (2 CH), 131.8 (C), 143.9 (C), 145.0 (C), 158.9 (C), 157.3 (C=O), 166.4 (C=O), 170.8 (C=O) ppm. Anal. Calcd for $C_{25}H_{22}N_2O_7$ (462.46): C 64.93, H 4.79, N 6.06; Found: C 64.53, H 4.62, N 6.32.

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

0.71 g (82%). Pale orange powder. M.p. 205-208° C. IR (KBr): 3352, 2728, 1711, 1510, 1443, 1338, 1236 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ 3.44 (*s*, MeN), 3.77 (*s*, MeO), 3.85 (*s*, MeO), 5.10 (*s*, OH), 5.99 (*s*, CH), 7.12 (*t*, ^3J = 7.4, CH), 7.26 (*t*, ^3J = 7.2, CH), 7.32 (*d*, ^3J = 7.3, 2 CH), 7.47 (*t*, ^3J = 7.3, CH), 7.86 (*t*, ^3J = 7.2, 2 CH), 7.98 (*d*, ^3J = 7.2, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 35.2 (MeN), 53.5 (MeO), 53.6 (MeO), 90.4 (CH), 116.1 (C), 120.8 (C), 124.0 (CH), 129.6 (CH), 134.1 (2 CH), 135.8 (CH), 136.5 (C), 139.7 (CH), 142.6 (2 CH), 131.4 (CH), 131.8 (C), 136.5 (C), 143.9 (C), 145.0 (C), 154.8 (C=O), 166.2 (C=O), 170.8 (C=O) ppm. Anal. Calcd for $C_{23}H_{20}N_2O_7$ (436.42): C 63.30, H 4.62, N 6.42; Found: C 63.53, H 4.45, N 6.52.

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

Yield: 0.72 g (80%). Pale yellow powder. M.p. 203-206°C. IR (KBr): 3372, 2918, 1721, 1513, 1453, 1328, 1216 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.27 (*t*, Me), 3.81 (*s*, CH_2N), 3.77 (*s*, MeO), 3.85 (*s*, MeO),

5.10 (*s*, OH), 5.99 (*s*, CH), 6.86 (*t*, ^3J = 7.4, CH), 6.91 (*t*, ^3J = 7.2, CH), 6.98 (*d*, ^3J = 7.3, 2 CH), 7.18 (*t*, ^3J = 7.3, CH), 7.24 (*t*, ^3J = 7.2, 2 CH), 7.94 (*d*, ^3J = 7.2, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 16.0 (Me), 35.2 (CH_2N), 53.5 (MeO), 53.6 (MeO), 90.4 (CH), 116.1 (C), 120.8 (C), 124.0 (CH), 129.6 (CH), 134.1 (2 CH), 135.8 (CH), 136.5 (C), 139.7 (CH), 142.6 (2 CH), 131.4 (CH), 131.8 (C), 136.5 (C), 145.0 (C), 158.9 (C), 157.6 (C=O), 167.2 (C=O), 170.8 (C=O) ppm. MS: *m*/*z* (%) = 450 (15) [M^+], 435 (64), 420 (75), 419 (100), 388 (50), 31 (28). Anal. Calcd for $C_{24}H_{22}N_2O_7$ (450.44): C 64.00, H 4.92, N 6.22; Found: C 64.33, H 4.55, N 5.92.

References

[1] Tietze, L. F.; Brasche, C.; Gericke, K. M. *Domino Reactions in Organic Synthesis*, Wiley-VCH Press, **2006**.
[2] Ho, T. *Challenges in Synthetic Organic Chemistry*, Clarendon Press: Oxford, **1990**.
[3] Ho, T. L. *Tandem Organic Reactions*, John Wiley & Sons, New York, **1992**.
[4] Ho, T. L. *Tactics of Organic Synthesis*, John Wiley & Sons, New York, **1994**.
[5] Serratosa, F.; Xicart, J. *Organic Chemistry in Action: The Design of Organic Synthesis*, Elsevier: New York, **1996**.
[6] Smith, W. A.; Bochkov, A. F.; Caple, R. *Organic Synthesis: The Science behind the Art*, Royal Society of Chemistry: Cambridge, U.K., **1998**.
[7] *Cao*, H.; Zhan, H.; Lin, Y.; Lin, X.; Du, Z.; Jiang, H. *Org. Lett.*, **2012**, *14* , 1688.
[8] Xue, N.; Yang, X.; Wu, R.; Chen, J.; He, Q.; Yang, B.; Lu, X.; Hu, Y. *Bioorganic & Medicinal Chemistry*, **2008**, *16*, 2550.
[9] Sączewski, F.; Dębowski, T.; Petrusewicz, J.; Gdaniec, M.; Dąbrowski, R. K.; Nowakowska, E. *Il Farmaco*, **2000**, 55, 56.
[10] Luo, L.; Zhao,Y.; Lu, Y.; Okamura, T.; Sun, W. *Polyhedron*, **2012**, *38*, 88.
[11] Heeres, J.; Backx, L. J. J.; Mostmanns, J. H.; Cutsem, V. J. *J. Med. Chem.*, **1979**, *22*, 1003.
[12] Hunkeler, W.; M€ohler, H.; Pieri, L.; Polc, P.; Bonetti, E. P.; Cumin, R.; Schaffner, R.; Haefely,W. *Nature*, **1981**, *290*, 514.