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A Novel Three-Component One-Pot Pyrimidine Synthesis Based upon a Coupling–Isomerization Sequence†

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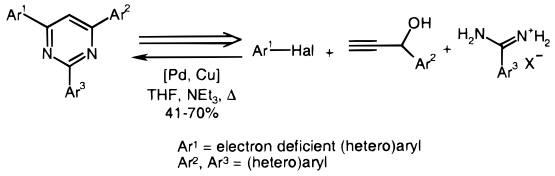
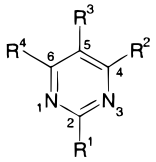
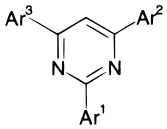
ABSTRACT



2,4,6-Tri(hetero)aryl-substituted pyrimidines can be readily synthesized in a three-component one-pot process based upon a coupling–isomerization sequence of an electron-poor (hetero)aryl halide and a terminal propargyl alcohol subsequently followed by a cyclocondensation with amidinium salts.

The pyrimidyl heterocyclic core **1** is a widespread subunit in numerous natural products and, ultimately, in the pyrimidine and purine bases as constituting the ribo- and deoxyribonucleosides.[1] Besides the strong deactivation of pyrimidines toward electrophilic substitution and the facilitated reactivity in nucleophilic additions and substitutions,[1a,f,2] this class of heterocycles could become increasingly important as an interesting structural coordinating substitute ligand for pyridyl units in supramolecular metallo-gridlike architectures[3] and in novel inorganic/organic hybrid types of molecular wires.[4]





Furthermore, a number of synthetic pharmacophores with antibacterial,[5] antimicrobial, antifungal,[6] and antimycotic[7] activities are based upon the pyrimidyl structural motifs **1** and **2**.

† In memoriam, Professor Dr. Rudolf Gompper (1926−1999).

(1) For reviews, see: (a) Brown, D. J. In *The Chemistry of Heterocyclic Compounds, Vol. 16, The Pyrimidines*; Weissberger, A., Ed.; Wiley-Interscience: New York, 1970. (b) Lister, J. H. In *The Chemistry of Heterocyclic Compounds, Vol. 24, Fused Pyrimidines, Part II, The Purines*; Weissberger, A.; Taylor, E. C., Eds.; Wiley-Interscience: New York, 1971. (c) Hoffmann, M. G. In *Houben-Weyl, Methoden der Organischen Chemie, Vol. E9;* Schaumann, E., Ed.; G. Thieme Verlag: Stuttgart, 1996. (d) Hurst, D. T. In *An Introduction to the Chemistry and Biochemistry of Pyrimidines, Purines and Pteridines*; Wiley: Chichester, 1980. (e) Bojarski, J. T.; Mokrosz, J. L.; Bartón, H. J.; Paluchowska, M. H. *Adv. Heterocycl. Chem.* **1985**, *38*, 229. (f) Brown, D. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, New York, Toronto, Sydney, Paris, Frankfurt, 1984; Vol. 3, Chapter 2.13.

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(6) El-Hashash, M. A.; Mahmoud, M. R.; Madboli, S. A. *Indian J. Chem., Sect. B* **1993**, *32B*, 449.

(7) Keutzberger, A.; Gillessen, J. *Arch. Pharm. (Weinheim, Ger.)* **1985**, *318*, 370.

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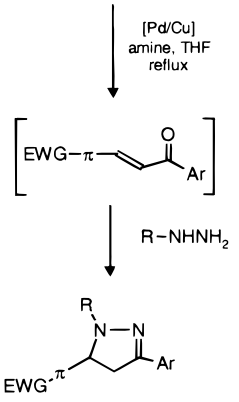
Synthetically, condensation reactions of 1,3-dicarbonyl compounds (and synthetic equivalents) with amidines or amidinium salts allow a broad access to substituted pyrimidines **1**.[2,8] However, pyrimidines with a 2,4,6-triaryl substitution pattern (**2**) are constructed in stepwise procedures.[2]

Therefore, we set out to develop a novel pyrimidine synthesis, preferentially in a straightforward highly convergent manner, that also can be conducted as a one-pot process. Here, we wish to communicate a facile one-pot synthesis of 2,4,6-tri(hetero)aryl-substituted pyrimidines (**2**) based upon a coupling−isomerization sequence with a subsequent cyclocondensation/aromatization with amidinium salts.

Recently, we found that palladium/copper-catalyzed cross-coupling reactions of electron-poor halogen-substituted π-systems and 1-aryl prop-2-yn-1-ols do not furnish the expected propargyl alcohols but rather give the isomeric enone components.[9] Mechanistically, this isomerization occurring after the cross-coupling reaction is purely base-catalyzed and opens a new access to electron-deficient propenones. With this powerful tool for the construction of chalcones (1,3-diaryl propenones) in hand and considering the mild reaction conditions for the Sonogashira coupling reaction, we have developed a novel one-pot pyrazoline synthesis (Scheme 1).[9]

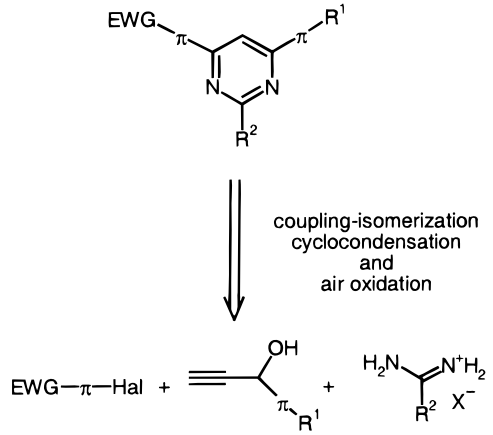
Scheme 1. One-Pot Pyrazoline Synthesis Based upon a Coupling−Isomerization Sequence



EWG: electron withdrawing group

Since the cyclocondensation of amidinium salts with chalcones (1,3-diaryl propenones) to give pyrimidines is a well documented reaction,[10] retrosynthetically, an extension of the coupling−isomerization-based methodology to the synthesis of pyrimidines can be easily envisioned. Upon cyclocondensing amidines or amidinium salts as suitable 1,3-dinucleophilic components with the initially formed enone functionality, followed by a subsequent oxidative aromatization of the intermediate dihydropyrimidines, pyrimidines are readily formed (Scheme 2). In particular, the mild

Scheme 2. Retrosynthetic Concept for a Three-Component Pyrimidine Synthesis



reaction conditions of Sonogashira couplings[11] not only allow the presence of sensitive functional groups without tedious protection and deprotection steps but also are advantageous for base-mediated processes such as cyclocondensations. In addition, this strategy could also be extended to a combinatorial approach to 2,4,6-triaryl-substituted pyrimidines (**2**).

Thus, we have submitted *p*-iodo nitrobenzene (**3a**) or 4-bromo pyridine (**3b**), several aryl propynols **4**,[12] and amidinium salts **5**[13] to the reaction conditions of the Sonogashira coupling in a boiling mixture of triethylamine and THF.[14] In all cases the isolated products were the beige-to-yellow pyrimidines **6** in 41−70% yield (Table 1).[15] In neither case was the expected dihydropyrimidine found, regardless of whether the reaction has been performed under an anaerobic or aerobic atmosphere. As already shown for the one-pot synthesis of pyrazolines, the electron-withdraw-

(8) For an efficient repetitive synthesis of (oligo)pyrimidines based upon vinamidinium salt amidine condensations, see: Gompper, R.; Mair, H.-J. Polborn, K. *Synthesis* **1997**, 696

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(10) (a) Dodson,; Seyler, *J. Org. Chem.* **1951**, *16*, 461. (b) Al-Hajjar, F. H.; Sabri, S. S. *J. Heterocycl. Chem.* **1982**, *19*, 1087. (c) Simon, D.; Lafont, O.; Farnoux, C. C.; Miocque, M. *J. Heterocycl. Chem.* **1985**, *22*, 1551. (d) Boykin, D. W.; Kumar, A.; Bajic, M.; Xiao, G.; Wilson, W. D.; Bender, B. C.; McCurdy, D. R.; Hall, J. E.; Tidwell, R. R. *Eur. J. Med. Chem.* **1997**, *32*, 965.

(11) (a) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, H. *Synthesis* **1980**, 627. (b) Sonogashira, K. In *Metal Catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; p 203.

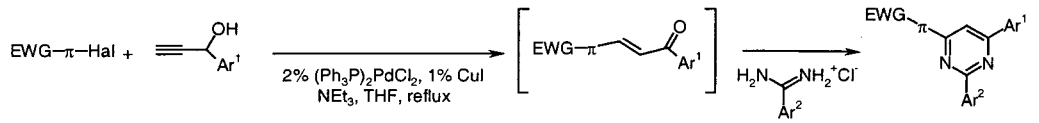
(12) The propynols **4** were synthesized according to Krause, N.; Seebach, D. *Chem. Ber.* **1987**, *120*, 1845.

(13) The amidinium salts **5** were synthesized according to a modification of the Pinner reaction; see: Schaefer, F. C.; Peters, G. A. *J. Org. Chem.* **1961**, *26*, 412.

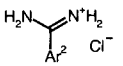
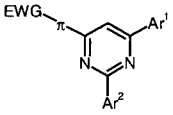
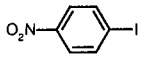
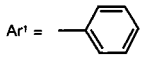
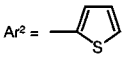
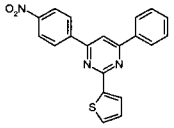
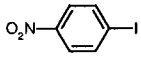
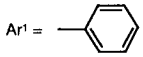
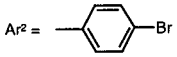
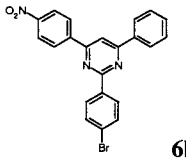
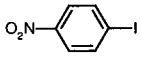
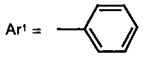
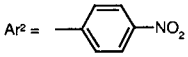
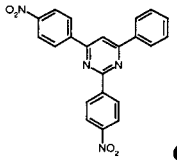
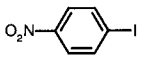
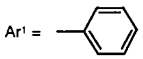
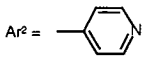
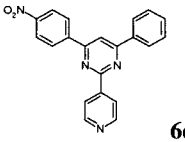
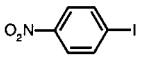
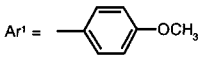
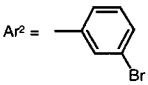
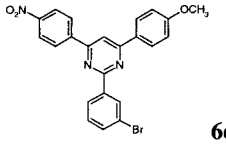
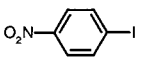
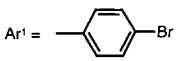
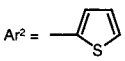
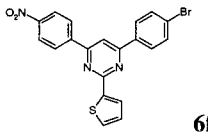
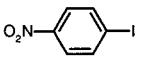
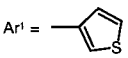
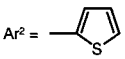
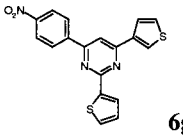
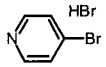
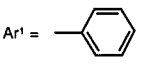
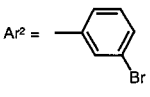
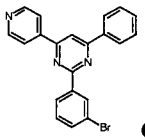
(14) **Typical Procedure (6g, entry 7).** To a magnetically stirred solution of 0.25 g (1.00 mmol) of 4-iodo nitrobenzene (**3a**), 22 mg (0.02 mmol) of $Pd(PPh_3)_2Cl_2$, and 2 mg (0.01 mmol) of CuI in a degassed mixture of 10 mL of THF and 5 mL of triethylamine under nitrogen was added a solution of 145 mg (1.05 mmol) of 1-(3-thienyl)-propyn-1-ol (**4d**) in 10 mL of THF dropwise at room temperature over a period of 30 min. The mixture was heated to reflux temperature for 16 h. After the mixture cooled to room temperature, 165 mg (1.00 mmol) of 2-thienyl amidinium chloride (**5a**) was added and the reaction mixture was heated to reflux temperature for 48 h. After cooling the solvents were removed in vacuo, and the residue was dissolved in dichloromethane and filtered through a short pad of silica gel. The solvents were evaporated in vacuo, and the residue was recrystallized from dichloromethane/pentane to give 255 mg (70%) of analytically pure **6a** as a beige powder.

(15) All compounds have been characterized spectroscopically and by correct elemental analysis.

Table 1. Three-Component Pyrimidine Synthesis Based upon a Coupling−Isomerization−Cyclocondensation Sequence[a]



3 **4** **5** **6** (41-70 %)

Entry	EWG-π-Hal **3**	Propargyl alcohol **4**	Amidinium salt **5**	Pyrimidine **6** (Yield %)[b]
				
1	 **3a**	 **4a**	 **5a**	 **6a** (57 %)
2	 **3a**	 **4a**	 **5b**	 **6b** (56 %)
3	 **3a**	 **4a**	 **5c**	 **6c** (46 %)
4	 **3a**	 **4a**	 **5d**	 **6d** (51 %)
5	 **3a**	 **4b**	 **5e**	 **6e** (50 %)
6	 **3a**	 **4c**	 **5a**	 **6f** (56 %)
7	 **3a**	 **4d**	 **5a**	 **6g** (70 %)
8	 **3b**	 **4a**	 **5e**	 **6h** (41 %)

[a] Reaction conditions: 1.0 equiv of the (hetero)aryl halide **3**, 1.05 equiv of the propargyl alcohol **4**, 0.02 equiv of $(Ph_3P)_2PdCl_2$, 0.01 equiv of CuI, 1.0 equiv of the amidine hydrochloride **5**; THF/NEt_3 2:1 (10 mL/mmol halide). [b] Yields refer to isolated yields of compounds **6** after recrystallization estimated to be ≥95% pure as determined by NMR spectroscopy and elemental analysis.

ing nature of the (hetero)aryl halide **3** is crucial for the successful coupling−isomerization step.[9] However, the substituents Ar^1 and Ar^2 on the pyrimidine ring can be electron-rich (entry 5), electron-poor (entries 3 and 4), or heterocyclic

(entries 1, 4, 6, and 7), and even bromo substituents are tolerated (entries 2, 5, 6, and 8).

The proton and carbon NMR spectroscopic data support the formation of the pyrimidine core, in particular, in the ^{1}H NMR spectra of **6** by the indicative appearance of the singlet for the methine proton at C5 of the central pyrimidine ring between δ 7.9 and 8.2. Furthermore, in the ^{13}C NMR spectra three quaternary signals can be found between δ 162 and 166, characteristic for sp^2-hybridized quaternary carbon centers adjacent to nitrogen atoms.[16] The signals at lowest field (δ 165 to 166) can be assigned to the C2 center, i.e., the amidine-type carbon atoms.[16]

In conclusion, we could show that the mild reaction conditions of the coupling−isomerization sequence of electron-poor (hetero)aryl halides with 1-aryl propargyl alcohols giving rise to chalcones can be extended to a one-pot three-component synthesis of 2,4,6-tri(hetero)aryl pyrimidines. Since 2-pyridyl-substituted pyrimidines are bidentate ligands for many late transition metals,[3,4] ultimately a one-pot ligand synthesis with subsequent complexation under self-organization to oligometallic chains and grids can be easily envisioned. Further studies directed to extend the one-pot pyrimidine synthesis to dendritic and self-organizing structures are currently underway.

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(16) Kalinowski, H.-O.; Berger, S.; Braun, S. *^{13}C NMR Spektroskopie*; Georg Thieme Verlag: Stuttgart, New York, 1984; p 351.