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Tandem synthesis of 1-(alkylamino)-2,4-diarylpyrimido[6,1-*a*]isoquinolin-5-ium chlorides from isoquinoline, *N*-alkyl-benzimidoyl chlorides, and isocyanides

Issa Yavari *, Gholamhossein Khalili, Anvar Mirzaei

Chemistry Department, Tarbiat Modares University, PO Box 14115-175, Tehran, Iran

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ABSTRACT

1-(Alkylamino)-2,4-diarylpyrimido[6,1-*a*]isoquinolin-5-ium chlorides are obtained in good yields via a tandem reaction between isoquinoline, *N*-alkyl-benzimidoyl chlorides and alkyl isocyanides in anhydrous acetonitrile.

Tandem reactions (TRs) that require in situ generation of reactive species are a special type of organic reaction in which the products are formed by sequential reactions.[1–5] Numerous organic transformations are the result of TRs. In fact, tandem processes lead to skeletal changes rather than merely functional group transformations. The secondary reaction for which the structural prerequisite is absent in the initial substrate must be triggered by the first reaction. TRs have become an increasingly active area of research yielding novel chemical scaffolds for drug discovery efforts.

Isoquinoline-fused pyrimidines are interesting as physiologically active compounds. In spite of investigations, there has been no report on the addition of isoquinoline to imidoyl chlorides.[6] In view of our continued interest in the chemistry of pyrimido[6,1-*a*]isoquinolinium salts, we have explored the reaction of isocyanides **3** with the reactive intermediates generated from isoquinoline (**2**), and *N*-alkyl-benzimidoyl chlorides **1** (prepared in situ from the corresponding amides, triphenylphosphine and CCl_4) to give 1-(alkylamino)-2,4-diarylpyrimido[6,1-*a*]isoquinolin-5-ium chlorides **4**. Our results are described in this Letter (Scheme 1).[7]

The structures of compounds **4** were assigned on the basis of spectroscopic data. The ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of 1-(alkylamino)-2,4-diarylpyrimido[6,1-*a*]isoquinolin-5-ium chlorides **4**. Any product other than isoquinolinium salts **4** could not be detected by ^{1}H NMR spectroscopy.

The ^{1}H NMR spectrum of **4a** exhibited four sharp singlets readily recognized as arising from *t*-butyl (δ = 1.30), methyl (δ = 2.19 and 2.41), and NH (δ = 5.63) protons along with characteristic resonances for the aromatic systems. The ^{13}C NMR spectrum of **4a** showed 20 distinct resonances in the aromatic region in agreement with the proposed structure. The mass spectra of these compounds displayed molecular ion peaks corresponding to the loss of chloride.

Mechanistically, the reaction may proceed via the initial formation of *N*-alkyl-benzimidoyl chloride **1**, generated from the corresponding *N*-alkyl-benzamides and CCl_4/PPh_3, followed by trapping with isoquinoline (**2**) to give the intermediate **5** (see Scheme 2). Nucleophilic attack of the isocyanide[8–10] **3** on intermediate **5** leads to an adduct **6**, which is deprotonated by a second molecule of isoquinoline to generate zwitterion **7**. Intermediate **7** undergoes cyclization and a 1,3-H shift to produce the dihydro intermediate **9**. This intermediate is converted into the pyrimido[6,1-*a*]isoquinolinium chloride **4** in the presence of isoquinolinium chloride, which acts as an oxidizing agent.

In summary, we have reported the synthesis of 1-(alkylamino)-2,4-diarylpyrimido[6,1-*a*]isoquinolin-5-ium chlorides via a tandem reaction between isoquinoline, *N*-alkyl-benzimidoyl chlorides, and alkyl isocyanides in anhydrous MeCN. The present procedure has the advantage that the reactants can be mixed without any prior activation or modification. The tandem nature of the present procedure makes it an interesting alternative to multi-step approaches

* Corresponding author. Tel.: +98 21 82883465; fax: +98 21 82883455.
E-mail address: yavarisa@modares.ac.ir (I. Yavari).

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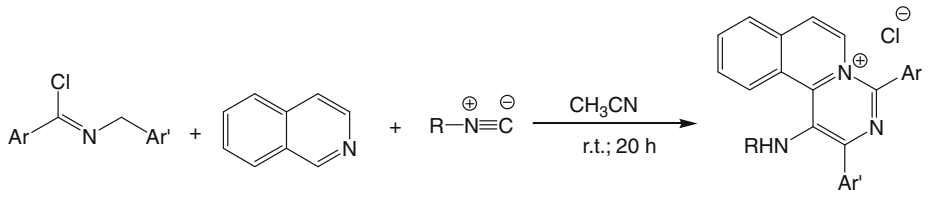
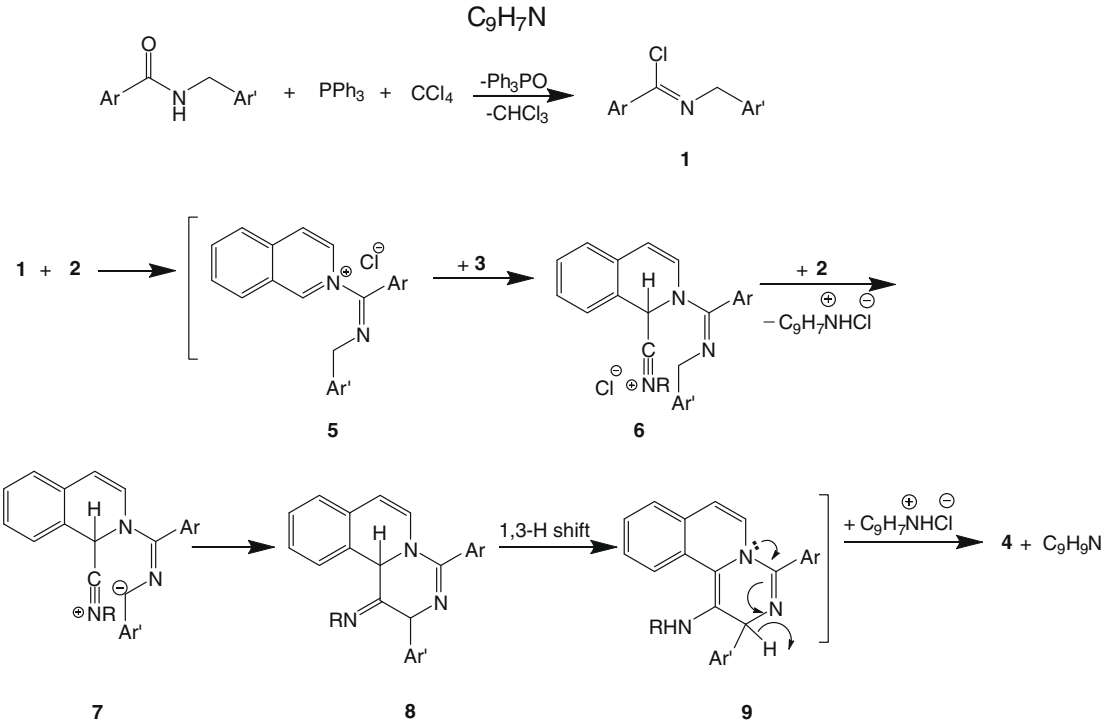


1	Ar	Ar'
a	4-MeC_6H_4	4-MeC_6H_4
b	4-MeC_6H_4	Ph
c	Ph	4-MeC_6H_4
d	4-ClC_6H_4	Ph
e	Ph	Ph

3	R
a	*t*-Bu
b	cyclohexyl

4	Ar	Ar'	R	Yield (%)
a	4-MeC_6H_4	4-MeC_6H_4	*t*-Bu	73
b	4-MeC_6H_4	Ph	*t*-Bu	75
c	Ph	4-MeC_6H_4	*t*-Bu	80
d	4-ClC_6H_4	Ph	*t*-Bu	72
e	Ph	Ph	*t*-Bu	77
f	4-MeC_6H_4	Ph	cyclohexyl	78
g	4-ClC_6H_4	Ph	cyclohexyl	70
h	4-MeC_6H_4	4-MeC_6H_4	cyclohexyl	74

Scheme 1.



Scheme 2.

and it may be considered as a practical route for the synthesis of pyrimido[6,1-*a*]isoquinolinium salts. Further investigations on the present method will be required to establish its scope and limitations.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tetlet.2009.12.097.

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7. *General procedure for the preparation of 1-(alkylamino)-2,4-diarylpyrimido[6,1-a]isoquinolinium chlorides* **4**: carbon tetrachloride (0.17 g, 1.1 mmol) was added to a mixture of Ph_3P (0.31 g, 1.2 mmol) and *N*-alkyl-benzamide (1 mmol) in anhydrous MeCN. The resulting solution was stirred at rt for 3 h. After the addition of isoquinoline (0.13 g, 1 mmol), stirring was continued for 2 h. This was followed by the addition of isocyanide **3** (1 mmol), and isoquinoline (0.13 g, 1 mmol) and stirring for an additional 15 h. The solvent was then evaporated under vacuum and the residue was washed with hot AcOEt and AcOEt–MeOH (10:1) to give **4**.
1-(tert-Butylamino)-2,4-di-p-tolylpyrimido[6,1-a]isoquinolin-5-ium chloride (**4a**): yellow powder, mp (decomp.): 210–212 °C. IR (KBr) (ν_{max}/cm^{-1}): 3405 (NH), 1645, 1609, 1577, 1491, 1463, 1388, 1358, 1217, 831, 802, 771, 696. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.30 (9H, s, CMe_3), 2.19 (3H, s, Me), 2.41 (3H, s, Me), 5.63 (1H, s, NH), 6.73 (2H, d, ^3J = 7.9 Hz, CH), 6.96 (2H, d, ^3J = 8.1 Hz, CH), 7.37 (1H, d, ^3J = 7.5 Hz, CH), 7.40–7.46 (2H, m, CH), 7.63–7.79 (5H, m, CH), 7.89 (1H, d, ^3J = 7.9 Hz, CH), 8.95 (1H, d, ^3J = 7.9 Hz, CH). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 30.80 (CMe_3), 48.4 (C), 57.7 (Me), 58.6 (Me), 118.3 (CH), 118.5 (CH), 119.5 (2 CH), 120.9 (CH), 122.4 (C), 123.6 (C), 125.1 (CH), 127.6 (2 CH), 128.6 (C), 128.7 (CH), 129.7 (2 CH), 129.8 (C), 130.1 (C), 130.2 (C), 130.8 (2 CH), 131.5 (C), 132.7

(CH), 135.4 (C), 137.7 (C), 143.2 (C). MS (EI), *m*/*z* (%): 433 $[M-Cl+H]^+$ (25), 376 (50), 329 (28), 273 (30), 155 (100), 129 (50), 105 (65), 77 (20), 41 (23). Anal. Calcd for $C_{30}H_{30}N_3Cl$ (468.02): C, 76.98; H, 6.46; N, 8.98. Found: C, 76.85; H, 6.34; N, 8.93.

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