Tetrahedron Letters 52 (2011) 5774–5776

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A novel one-pot domino reaction for the synthesis of 2-acetyl-3-(phenylamino)indolizine-1-carboxamide derivatives

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ARTICLE INFO

Article history:
Received 22 June 2011
Revised 5 August 2011
Accepted 19 August 2011
Available online 26 August 2011

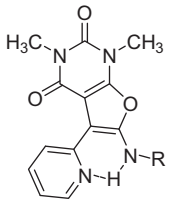
Keywords:
Indolizine derivatives
Isocyanide
Pyridine-2-carbaldehyde
Acetoacetanilide
One-pot reaction

ABSTRACT

2-Acetyl-3-(phenylamino)indolizine-1-carboxamide derivatives were obtained via a one-pot domino reaction of alkyl or aryl isocyanides and pyridine-2-carbaldehyde in the presence of acetoacetanilide in toluene without any prior activation or modification.

A number of heterocyclic compounds have been shown to possess pharmacological activities. Indolizines are such as example, which contain a ring junction nitrogen and are very rare in nature. Indolizines are structurally and chemically isomeric with indoles. It is this analogy between indoles and indolizines that has prompted speculation that indolizine analogs of biologically important indoles could conceivably have potent physiological activity.[1,2]

Many modifications, observations, and investigations have been reported in this area. Several indolizines were reported to possess biological activities including anti-inflammatory[3] and hypoglycemic[4,5] activities. In addition, 5HT3 receptor antagonist,[6] antiacetylcholine,[7] CNS depressant,[8] estrogen receptor binding,[9] anti-oxidant,[10,11] antimicrobial,[12] and analgesic activities have been described.[13] Many amino acid derivatives with an active indolizine nucleus have been utilized in cancer therapy.[14,15] A few substituted indolizines have been reported to have anti-tubercular activities.[16] Recently, various combinatorial routes to substituted indolizines have been reported.[17] In continuation of our investigations on isocyanide-based multicomponent reactions (IMCRs)[18–26] we have described the synthesis of furo[2,3-*d*]pyrimidine derivatives **1** from isocyanides, pyridinecarbaldehyde derivatives, and 1,3-dimethylbarbituric acid[27] (Fig. 1).



1

Figure 1. Furo[2,3-*d*]pyrimidine derivatives.

In the present work, we describe an efficient synthesis of the unexpected 2-acetyl-3-(phenylamino)indolizine-1-carboxamides **5a–d** via a new, one-pot, three-component reaction between pyridine-2-carbaldehyde (**2**) and acetoacetanilide (**3**) in the presence of isocyanides **4**.[28] It should be noted that this is the first report on the synthesis of 2-acetyl-3-(phenylamino)indolizine-1-carboxamide derivatives using multicomponent conditions. Analysis of the IR, ^{1}H and ^{13}C NMR spectral, mass spectrometric, elemental analyses, and single-crystal X-ray data confirm the formation of 2-acetyl-3-(phenylamino)indolizine-1-carboxamide **5a–d** in excellent yields without any prior activation or modification (Scheme 1).

The structures of products **5a–d** were assigned on the basis of spectroscopic analysis. The ^{1}H NMR spectrum of **5a** exhibited two sharp singlets at 1.56 and 2.56 ppm due to the *tert*-butyl and

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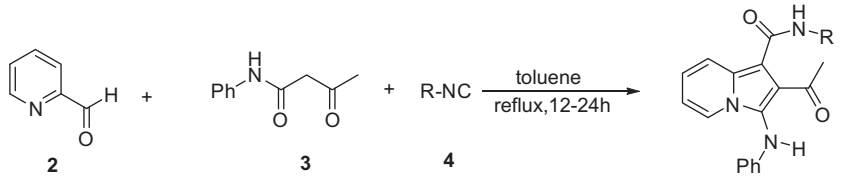
doi:10.1016/j.tetlet.2011.08.118



Product	R	Yield (%)
5a	*t*-Bu	92
5b	cyclohexyl	94
5c	2,6-dimethylphenyl	87
5d	benzyl	90

Scheme 1. Synthesis of 2-acetyl-3-(phenylamino)indolizine-1-carboxamides **5a–d** via a three-component condensation.

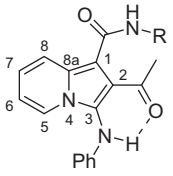


Figure 2. Intramolecular hydrogen bonding in compounds **5a–d**.

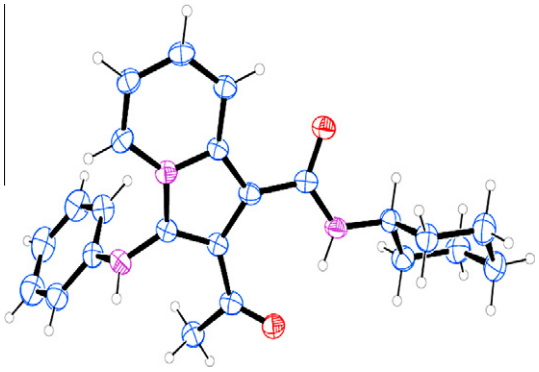
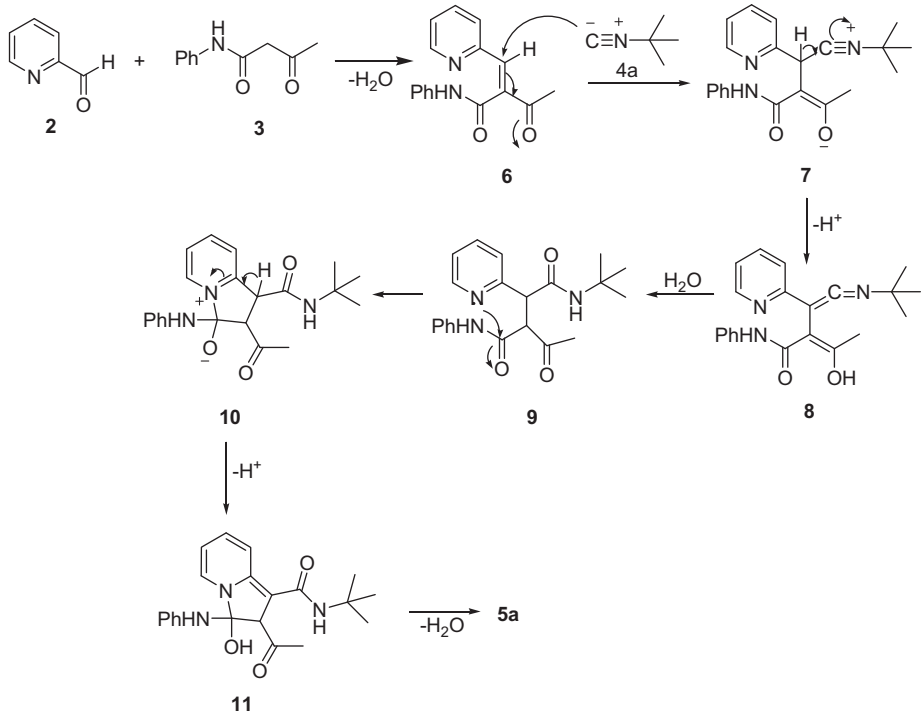


Figure 3. ORTEP diagram of **5b**.



Scheme 2. A speculative proposed mechanism for the formation of product **5a**.

methyl groups, respectively. Two NH protons appeared at 6.76 and 8.69 ppm (broad signal). This is rationalized through the formation of an intramolecular hydrogen bond in compounds **5a–d** resulting in a deshielding effect on the NH moiety causing the PhNH proton to be shifted downfield (Fig. 2).

The ^{1}H decoupled ^{13}C NMR spectrum of **5a** showed three signals readily recognized as arising from the three methyls of the *tert*-butyl (29.04 ppm), the methyl group (31.01 ppm) and the *tert*-butyl carbon (51.14 ppm) as well as 14 other distinct resonances in agreement with the proposed structure (see Ref. [28]). Unambiguous evidence for the structure of **5b** was obtained from single crystal X-ray analysis (Fig. 3).

A speculative mechanistic explanation for this reaction is provided in Scheme 2. The first step may involve a Knovenagel condensation between pyridine-2-carbaldehyde (**2**) and acetoacetanilide (**3**) leading to the formation of the stable intermediate enone **6**. This undergoes nucleophilic attack by isocyanide **4a** to generate adduct **7** which converts into **8** via H-transfer. Subsequently, **8** hydrolyzes to compound **9**. This adduct undergoes intramolecular cyclization via the pyridine nitrogen to afford compound **10** which converts into **11** by H-transfer. Compound **11** then eliminates H_2O to give the final compound **5a**.

In conclusion, we have reported the one-pot synthesis of 2-acetyl-3-(phenylamino)indolizine-1-carboxamide derivatives by an efficient and simple approach involving a three-component condensation between pyridine-2-carbaldehyde, acetoacetanilide, and various isocyanides.

Acknowledgments

We gratefully acknowledge financial support from the Research Council of the University of Sistan and Baluchestan.

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28. *General procedure for the preparation of N-tert-butyl-2-acetyl-3-(phenylamino)indolizine-1-carboxamide (**5a**):* to a stirred solution of pyridine-2-carbaldehyde (**2**) (0.11 g, 1 mmol) and acetoacetanilide (**3**) (0.18 g, 1 mmol) in toluene (10 mL) was added, dropwise, *tert*-butylisocyanide (**4a**) (0.08 g, 1 mmol) over 10 min at ambient temperature. The mixture was allowed to reflux for 12 h. After complete conversion as indicated by TLC, the solvent was removed and the residue recrystallized from a mixture of EtOAc/*n*-hexane (1:5) to yield **5a**: dark green powder, yield 92%, (0.32 g); mp 181–183 °C, IR (KBr) (ν_{max}, cm^{-1}): 1600 and 1640 (C=O), 3244 and 3446 (N–H). MS (*m*/*z*, %): 349 (M$^+$, 57), 276 (100), 249 (15), 205 (66), 78 (72), 57 (74), 43 (76). ^{1}H NMR ($CDCl_3$, 400.2 MHz): δ_H 1.56 (9H, s, CMe_3), 2.56 (3H, s, CH_3), 6.50–7.23 (7H, m, CH_{arom}), 6.76 (1H, s, NH), 7.60 (1H, d, J = 7.2 Hz, CH-8), 8.40 (1H, d, J = 9.2 Hz, CH-5), 8.69 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ_C 29.04 (s, CMe_3), 31.01 (s, CH_3CO), 51.14 (s, $NCMe_3$), 106.91 (s, C-1), 113.39 (s, C-7), 113.72 (s, 2CH of phenyl), 119.83 (s, C-3), 120.03 (s, C-6), 121.44 (s, C-8), 122.14 (s, CH of phenyl), 122.15 (s, C-5), 125.54 (s, C-2), 129.79 (s, 2CH of phenyl), 132.48 (s, C-8a), 144.19 (s, C_{ipso} of phenyl), 164.83 (s, C=O of amide), 199.24 (s, C=O); Anal. Calcd for $C_{21}H_{23}N_3O_2$: C, 72.18; H, 6.63; N, 12.03. Found: C, 72.30; H, 6.52; N, 11.91.

2-Acetyl-N-cyclohexyl-3-(phenylamino)indolizine-1-carboxamide (**5b**): dark yellow powder, yield 94%, (0.35 g); mp 154–157 °C, IR (KBr) (ν_{max}, cm^{-1}): 1602 and 1653 (C=O), 3239 and 3446 (N–H). MS (*m*/*z*, %): 375 (M$^+$, 65), 276 (100), 249 (20), 205 (73), 93 (40). ^{1}H NMR ($CDCl_3$, 400.2 MHz): δ_H 1.23–2.07 (10H, m, $5CH_2$ of cyclohexyl), 2.57 (3H, s, CH_3), 4.03 (1H, br m, NCH of cyclohexyl), 6.50–7.22 (7H, m, CH_{arom}), 6.69 (1H, s, NH), 7.61 (1H, d, J = 7.2 Hz, CH-8), 8.40 (1H, d, J = 9.2 Hz, CH-5), 9.00 (1H, br d, J = 7.6 Hz, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ_C 24.83 (s, $2CH_2$ of cyclohexyl), 25.77 (s, CH_2 of cyclohexyl), 31.13 (s, CH_3CO), 33.11 (s, $2CH_2$ of cyclohexyl), 48.16 (s, NCH), 105.56 (s, C-1), 113.53 (s, C-7), 113.59 (s, 2CH of phenyl), 119.94 (s, C-3), 120.16 (s, C-6), 121.70 (s, C-8), 122.13 (s, CH of phenyl), 122.54 (s, C-5), 125.95 (s, C-2), 129.81 (s, 2CH of phenyl), 132.12 (s, C-8a), 144.26 (s, C_{ipso} of phenyl), 164.33 (s, C=O of amide), 199.44 (s, C=O); Anal. Calcd for $C_{23}H_{25}N_3O_2$: C, 73.57; H, 6.71; N, 11.19. Found: C, 73.69; H, 6.66; N, 11.09; X-ray data for compound **5b**: Emprical formula, $C_{23}H_{25}N_3O_2$, M_r = 375.47, triclinic, space group P-1, a = 7.0688(19) Å, b = 11.792(3) Å, c = 12.886(3) Å, α = 108.409(13)°, β = 101.563(13)°, γ = 90.574(13)°, V = 995.4(4)Å^3, Z = 2, F(000) = 400, D_x = 1.253 Mg/m^3, λ = 0.71073Å, θ = 2.6–25°, μ = 0.08 mm^{-1}, T = 200 K, crystal dimensions 0.39 × 0.04 × 0.02 mm. CCDC 830627 contains the supplementary crystallographic data for this compound.

2-Acetyl-N-(2,6-dimethylphenyl)-3-(phenylamino)indolizine-1-carboxamide (**5c**): dark green powder, yield 87%, (0.34 g); mp 114–117 °C, IR (KBr) (ν_{max}, cm^{-1}): 1603 and 1645 (C=O), 3194 and 3446 (N–H). MS (*m*/*z*, %): 397 (M$^+$, 25), 276 (95), 249 (40), 205 (34), 108 (100), 78 (89). ^{1}H NMR ($CDCl_3$, 400.2 MHz): δ_H 2.35 (6H, s, $ArMe_2$), 2.65 (3H, s, CH_3), 6.51–7.33 (10H, m, CH_{arom}), 7.05 (1H, s, NH), 7.74 (1H, d, J = 7.2 Hz, CH-8), 8.71 (1H, d, J = 9.6 Hz, CH-5), 10.92 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ_C 18.86 (s, $2CH_3$ of $ArMe_2$), 31.29 (s, CH_3CO), 104.72 (s, C-1), 113.57 (s, 2CH of phenyl), 113.84 (s, C-7), 119.96 (s, C-3), 120.65 (s, C-6), 122.28 (s, C-8), 122.41 (s, C-5), 123.43 (s, CH of phenyl), 126.52 (s, C-2), 127.84 (s, $2CH_{aryl}$), 128.27 (s, CH_{aryl}), 129.29 (s, 2CH of phenyl), 134.54 (s, C-8a), 135.19 (s, C_{ipso} of aryl), 135.36 (s, $2C_{aryl}$), 144.30 (s, C_{ipso} of phenyl), 163.50 (s, C=O of amide), 200.03 (s, C=O); Anal. Calcd for $C_{25}H_{23}N_3O_2$: C, 75.54; H, 5.83; N, 10.57. Found: C, 75.47; H, 5.91; N, 10.68.

2-Acetyl-N-benzyl-3-(phenylamino)indolizine-1-carboxamide (***5d***): green powder, yield 90%, (0.34 g); mp 186–189 °C, IR (KBr) (ν_{max}, cm^{-1}): 1596 and 1649 (C=O), 3226 and 3416 (N–H). MS (*m*/*z*, %): 383 (M$^+$, 11), 276 (42), 214 (54), 108 (100), 91 (94). ^{1}H NMR ($CDCl_3$, 400.2 MHz): δ_H 2.57 (3H, s, CH_3), 4.70 (2H, d, J = 5.6 Hz, CH_2 of benzyl), 6.37 (1H, s, NH), 6.49–7.52 (12H, m, CH_{arom}), 7.63 (1H, d, J = 7.2 Hz, CH-8), 8.61 (1H, d, J = 10.0 Hz, CH-5), 9.60 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ_C 31.23 (s, CH_3CO), 43.60 (s, CH_2 of benzyl), 105.09 (s, C-1), 113.67 (s, 2CH of phenyl), 113.85 (s, C-7), 120.34 (s, CH of phenyl), 120.55 (s, C-3), 122.60 (s, C-6), 123.74 (s, C-8), 125.64 (s, C-5), 126.52 (s, C-2), 127.11 (s, CH of phenyl), 127.81 (s, $2CH_2$ of phenyl), 128.61 (s, 2CH of phenyl), 129.92 (s, 2CH of phenyl), 133.56 (s, C-8a), 139.10 and 143.89 (2s, $2C_{ipso}$ of phenyl), 165.05 (s, C=O of amide), 199.43 (s, C=OC=O); Anal. Calcd for $C_{24}H_{21}N_3O_2$: C, 75.18; H, 5.52; N, 10.96. Found: C, 75.30; H, 5.45; N, 10.86.