ACS Combinatorial Science

Research Article

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One-Pot Access to a Library of Structurally Diverse Nicotinamide Derivatives via a Three-Component Formal Aza [3 + 3] Cycloaddition

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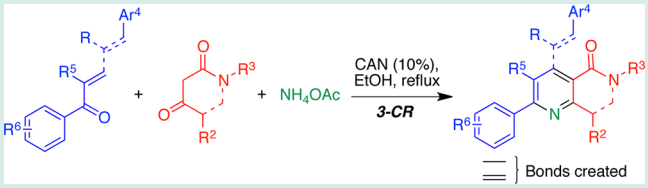
Supporting Information

ABSTRACT: The three-component formal [3 + 3] aza-annulation between chalcones, β-ketoamides, and ammonium acetate in the presence of CAN as a Lewis acid affords good to excellent yields of highly substituted nicotinamides or their fused derivatives. This transformation leads to the formation of one C−C and two C−N bonds in a single synthetic operation and involves up to five individual steps.



KEYWORDS: *multicomponent reactions, pyridine synthesis, [3 + 3]aza-annulations*

INTRODUCTION

Pyridine is one of the most important nitrogen heterocycles both in academic and industrial environments, and this has led to the development of a huge number of methods for its synthesis, which have been reviewed recently.[1−3] Besides their use as catalysts, as part of supramolecular scaffolds and in the preparation of new materials, pyridine derivatives are of interest mainly because of their plethora of biological activities. In fact, pyridine satisfies the definition "a single molecular framework able to provide ligands for diverse receptors", and therefore, it can be considered as a privileged structure in drug discovery.[4]

Nicotinic acid derivatives and, especially, nicotinamides constitute one of the most important families of biologically relevant compounds containing a pyridine ring. They are members of the B-vitamin group and play a key role in many essential metabolic processes. The NAD/NADP coenzymes are nicotinamide derivatives, leading to many potential targets for interference with drugs.[5] Besides, a number of derivatives of nicotinamide have demonstrated pharmacological activity at other types of targets. Thus, nicorandil is an established drug acting as a selective activator of ATP-dependent potassium channel that is employed in the treatment of cardiac ischemia.[6] Many other pharmacologically relevant nicotinamides have been described, including antiarrythmic compounds acting by inhibition of the sodium−calcium exchanger (NCX),[7] anti-cancer compounds acting by inducing apoptosis[8] or by inhibiting vascular endothelial growth factor (VEGF)-induced angiogenesis,[9] anxiolytic, and antidepressant activity associated to the inhibition of Type 5 metabotropic glutamate receptors (mGluR5)[10] and inhibitors of the gastric H^+/K^+ ATPase acting as antiulcer agents.[11]

Contemporary organic synthesis is driven by traditional concepts such as reactivity and selectivity, and also by economic and environmental concerns. In this connection, the need to optimize synthetic efficiency has led to the development of the concept of multibond forming reactions,[12] which achieve the generation of several bonds in a single operation, thereby minimizing intermediate purification operations and waste generation from organic solvents and chromatographic stationary phases. Multicomponent reactions (MCRs) are particularly important in this field and can be defined as convergent processes that combine three or more reagents in a single synthetic operation leading to a product that contains significant fragments of all components.[13,14] The development and application in synthesis of new multicomponent reactions is an important part of the research carried out in pharmaceutical companies for library preparation in the context of drug discovery[15−17] and, since heterocycles are key structural fragments of at least 60% of all known drugs and agrochemicals, the application of the MCR methodology in heterocycle synthesis can be considered crucial. While MCRs have been often applied to pyridine synthesis (for leading references, see refs 18 and 19) there is very little precedent for their use in the preparation of nicotinamides.[20] In this context, we report here a new multicomponent reaction that allows a very efficient preparation of highly substituted nicotinamides and their fused derivatives from simple, acyclic starting materials.

RESULTS AND DISCUSSION

Our method is based on the reaction between chalcones, β-ketoamides and ammonium acetate, as an ammonia source. The required chalcones (compounds **1**) were of commercial origin or were obtained by aldol condensation between phenones and benzaldehydes under standard conditions.[21−24] On the other hand, β-ketoamides were either obtained commercially or prepared by treatment of primary or secondary amines with 2,2,6-trimethyl-1,3-dioxin-4-one in conditions recently developed by our group that involve the presence of sodium acetate, which leads to the formation of an intermediate mixed anhydride and allows the use of milder temperature

Received: August 1, 2012
Revised: September 3, 2012
Published: September 6, 2012

   dx.doi.org/10.1021/co300081k | *ACS Comb. Sci.* 2012, 14, 551−557

conditions than alternative protocols.[25] β-Oxoanilides were also prepared by a literature method.[26]

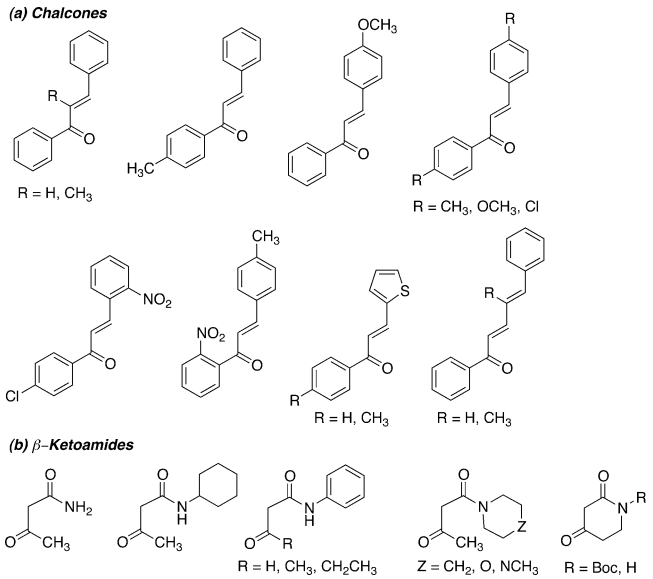


Figure 1. Building blocks employed in this work for the synthesis of nicotinamides.

With suitable starting materials in hand, we investigated the three-component reaction that constituted our goal. For the initial optimization study, we examined the reaction between chalcone, acetoacetamide and ammonium acetate. The first experiment (entry 1, Table 1) was performed in refluxing ethanol and in the presence of ceric ammonium nitrate because of our experience in the use of this reagent as a catalyst in a somewhat related tetrahydropyridine synthesis from β-dicarbonyl compounds, acrolein, and primary amines in the presence of ethanol[27−29] and provided a rather complex mixture of the desired compound **3a**, the corresponding dihydropyridine **4** and a small amount of compound **5**. The latter compound arises from the Robinson annelation between the chalcone and acetoacetamide without incorporation of ammonia, and was unambiguously identified by its independent synthesis from chalcone and acetoacetamide in the presence of piperidine.[30] While subsequent experiments showed that the use of a higher catalyst load (entry 2, Table 1) or a more concentrated solution (entry 3, Table 1) did not greatly improve the results, a longer reaction time (15 h) was found to be highly beneficial, leading almost exclusively to the target compound **3a** (entry 4, Table 1). A control experiment carried out under the same conditions but in the absence of catalyst also led to consumption of the starting materials and to the formation of **3a**, but in this case a higher amount of the side product **5** was observed (entry 5, Table 1). Therefore, subsequent experiments were performed in the presence of 10% CAN.

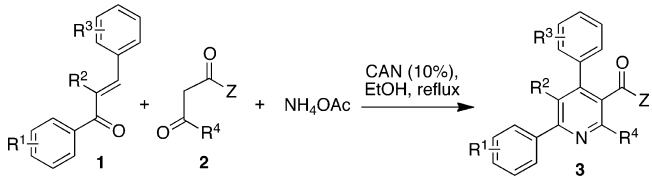
Table 1. Results Obtained under the Optimal Conditions in the Presence or Absence of CAN

entry	conditions	4/3a/5
1	CAN (10%), EtOH, reflux, 4 h	41:45:14
2	CAN (20%), EtOH, reflux, 4 h	30:55:15
3	CAN (10%), EtOH, reflux, 4 h[a]	40:48:12
4	CAN (10%), EtOH, reflux, 15 h	0:95:5
5	EtOH, reflux, 15 h	0:76:24

[a]2 M solution of the reagents (in all the other experiments, reagent concentration was 1 M).

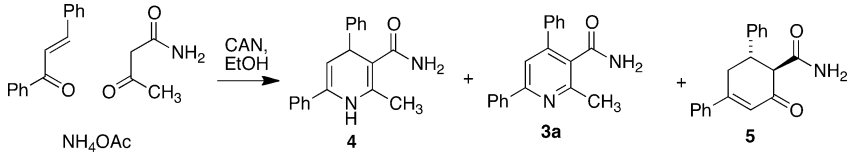
Having established the optimal conditions for nicotinamide synthesis, we undertook an exploration of the scope of the method. As shown in Scheme 2 and Table 2, the reaction normally proceeded in good to excellent yields, and tolerated well the presence of either electron-withdrawing or electron-releasing groups at the chalcone aromatic rings. Ortho-substitution at the R^1 substituent (compound **3h**) led to a decrease in yield due to steric hindrance, but it had little effect on the other aromatic ring (substituent R^3), as shown by the 85% yield obtained for compound **3g**. The main limitation of the method came from the presence of substituents different from hydrogen at R^2, which was clearly detrimental for yield and which could not be overcome in spite of having attempted many different conditions (compound **3i**). On the other hand, while R^4 was methyl in most cases due to a better accessibility of the starting materials, we verified that the presence of other substituents was also possible (compounds **3l−3n**). Finally, the amide nitrogen could be unsubstituted (compounds **3a−i**), monosubstituted with alkyl (**3j**) or aryl (**3k−n**) groups or disubstituted (**3o−q**). Compound **3a** had been prepared by a related two-component reaction starting from chalcone and 2-methylcrotonamide, albeit in a modest 36% yield.[31]

Scheme 2. Three-Component Synthesis of Nicotinamide Derivatives



To prove the ability of the method to introduce further structural diversity in the nicotinamide derivatives, we examined the preparation of compounds bearing substituents other than phenyl at the pyridine C-4 position by use of suitably modified chalcones. This way, we prepared compounds **3r** and **3s**, with a heterocyclic moiety at C-4, and **3t** and **3u**, with a styryl chain. In all these cases, the reaction time was 24 h and yields were around 70% (Figure 2).

Scheme 1. Products Observed during the Optimization Studies



dx.doi.org/10.1021/co300081k | ACS Comb. Sci. 2012, 14, 551−557

Table 2. Scope and Yields Obtained in the Synthesis of Substituted Nicotinamides

Cpd	R^1	R^2	R^3	R^4	Z	Time (h)	Yield (%)[a]
3a	H	H	H	CH_3	NH_2	15	92
3b	4-CH_3	H	H	CH_3	NH_2	15	95
3c	4-CH_3	H	4-CH_3	CH_3	NH_2	15	95
3d	H	H	4-OCH_3	CH_3	NH_2	15	95
3e	4-OCH_3	H	4-OCH_3	CH_3	NH_2	24	73
3f	4-Cl	H	4-Cl	CH_3	NH_2	24	95
3g	4-Cl	H	2-NO_2	CH_3	NH_2	15	85
3h	2-NO_2	H	4-CH_3	CH_3	NH_2	30	66
3i	H	CH_3	H	CH_3	NH_2	30[b]	20
3j	4-CH_3	H	4-CH_3	CH_3		24	83
3k	H	H	H	CH_3	NHPh	15	84
3l	H	H	H	C_2H_5	NHPh	32[b,c]	74
3m	H	H	H	C_3H_7	NHPh	15	82
3n	H	H	H	$CH(CH_3)_2$	NHPh	24[c]	74
3o	H	H	H	CH_3		24	64
3p	H	H	H	CH_3		24	80
3q	H	H	H	CH_3		24	67

[a]Isolated yields, after crystallization or chromatography. [b]Experiments carried out with 1:2:3 ratio of chalcone:β-ketoamide:ammonium acetate (+1 additional eq of ammonium acetate after 24 h). [c]Experiments carried out at 50 °C.

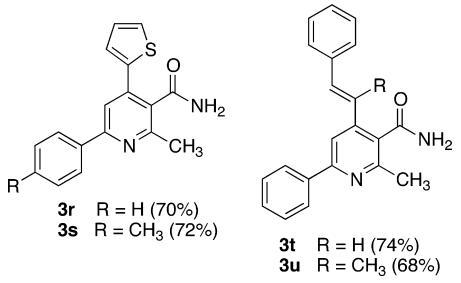
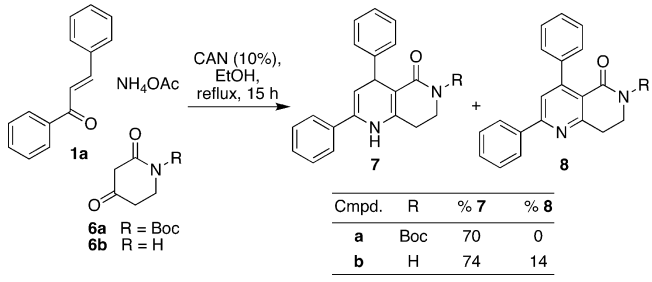


Figure 2. Additional nicotinamides bearing heterocyclic or styryl C-4 substituents.

Finally, we also examined briefly the preparation of fused pyridines by employing a β-ketolactam as the starting material. To this end, we prepared compounds **6** following a literature procedure[32] and studied their reaction with chalcone **1a** and ammonium acetate in refluxing ethanol. As shown in Scheme 3,

Scheme 3. Synthesis of Fused Dihydronicotinamide-Type Compounds from a β-Ketolactam

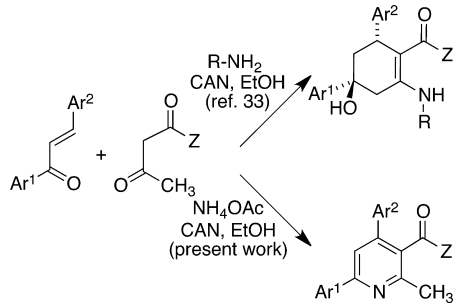


Cmpd.	R	% **7**	% **8**
a	Boc	70	0
b	H	74	14

in this case the main products were the 1,6-naphthyridine derivatives **7**, containing a fused dihydropyridine substructure, together with a small amount of the corresponding pyridine **8b** for R = H.

It is interesting to note that a similar reaction involving the use of primary amines instead of ammonia has been found to give cyclohexene derivatives rather than the pyridines obtained in the present work.[33] Thus, the exquisite balance between the two chemodivergent pathways involving [3 + 3] and aza-[3 + 3] formal cycloadditions, respectively, seems to depend on the steric hindrance of the nitrogen of the N-nucleophile (Scheme 4).

Scheme 4. Comparison between Our Three-Component Reaction and a Related One Starting from Primary Amines

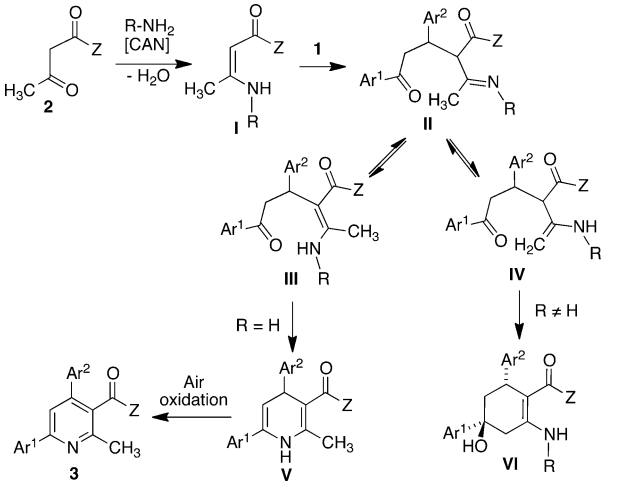


Mechanistically, both reactions are proposed to start by the generation of an intermediate β-enaminone **I** via the CAN-catalyzed reaction between the starting primary amine or ammonia and the β-dicarbonyl compound **2**. This assumption is based on two facts: (a) CAN catalysis is known to lead to the very fast formation of β-enaminones;[34] (b) control experiments carried out from an isolated enaminone (3-aminocrotonamide) led to a result that was identical to that of our three-component reactions. A Michael addition of **I** onto the enone fragment of chalcones **1** should lead to intermediate **II**, which would be in tautomeric equilibrium with two enamine species **III** and **IV**. In the case R = H, the unhindered nitrogen atom is able to attack the opposing carbonyl as a nucleophile, leading to dihydropyridine **V** after loss of a molecule of water, in a Hantzsch-like process. On the other hand, for the more hindered cases where R is different from hydrogen, the reaction with the side chain

dx.doi.org/10.1021/co300081k | ACS Comb. Sci. 2012, 14, 551−557

carbonyl is slower because of steric hindrance and the system tends to evolve via the less stable, but also more reactive, intermediate **IV**, which affords the cyclohexene derivatives **VI** (Scheme 5).

Scheme 5. Mechanistic Proposal That Accounts for the Results Described in This Paper



While dihydropyridines are normally reasonably stable, during the optimization studies, we never observed compounds **V** as the only reaction products but as part of mixtures with pyridines **3**, indicating that they are particularly prone to oxidation. Furthermore, a control experiment with an ester (Z = OEt) gave a stable dihydropyridine, which shows that this ease of oxidation has to be attributed to the presence of the amide substituent. This behavior can be attributed to the very strong conjugation between the amide carbonyl and its nitrogen, which makes the carbonyl less prone to accept electron density from the dihydropyridine nitrogen and hence makes the latter more electron-rich and the corresponding heterocycle more readily oxidizable. In the case of compounds **7**, the more rigid structure must hamper dehydrogenation by facilitating conjugation of the dihydropyridine nitrogen with the lactam carbonyl.

CONCLUSIONS

In conclusion, the CAN-catalyzed reaction between chalcones, β-ketoamides and ammonium acetate constitutes an excellent route to highly substituted nicotinamides, which can be extended to the preparation of their fused derivatives. These compounds have a 6-aryl substituent and lack a C-5 carbonyl function and hence are not readily accessible through traditional Hantzsch chemistry. This three-component reaction, which can be considered as a new application of [3 + 3] aza-annulations[35] to the generation of molecular diversity, leads to the formation of one C−C and two C−N bonds in a single synthetic operation and normally proceeds in good to excellent yield in spite of involving up to five individual steps.

EXPERIMENTAL PROCEDURES

General Procedure for the Synthesis of Nicotinamide Derivatives. To a stirred solution of the suitable 1,3-diphenyl-2-propen-1-one derivative (1 equiv, 1 mmol), the appropriate primary or secondary β-ketoamide derivative (1.1 equiv, 1.1 mmol) and ammonium acetate (3 equiv, 3 mmol) in ethanol (1 mL) was added ceric ammonium nitrate (CAN, 10% mol) and the resulting mixture was refluxed for the time given in table 2. After completion of the reaction (checked by TLC), the mixture was poured onto ice water (15 mL) and the precipitate formed was collected by filtration and washed with water. In some cases (compounds **3o−3q**, **7a**, **7b**, and **8b**), the cooled reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with water to remove CAN and the excess of ammonium acetate. The organic layer was then washed with brine and dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude residue was recrystallized from EtOH or purified by silica column chromatography, eluting with petroleum ether- ethyl acetate or chloroform-ethyl acetate mixtures, to give pure compounds **3**, **7**, or **8**.

2-Methyl-4,6-diphenylnicotinamide (3a): White solid; mp 219−221 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 8.05 (dd, J = 7.9, 1.6 Hz, 2H), 7.64−7.41 (m, 9H), 5.63 (bs, 1H), 5.40 (bs, 1H), 2.80 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.8, 157.4, 155.9, 147.7, 138.9, 138.3, 129.5, 129.0, 129.0, 128.9, 128.4, 127.3, 118.7, 23.1; IR (KBr) ν 3378, 3204, 1694, 1651, 1621, 1586, 1574, 1547, 1493, 1360, 778, 757, 694 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{16}N_2O$ C 79.14, H 5.59, N 9.72; found C 78.93, H 5.53, N 9.51.

2-Methyl-6-(4-methylphenyl)-4-phenylnicotinamide (3b): White solid; mp 248−250 °C; ^{1}H NMR (250 MHz, DMSO) δ = 8.06 (d, J = 7.8 Hz, 2H), 7.87 (s, 1H), 7.71 (s, 1H), 7.67−7.38 (m, 6H), 7.31 (d, J = 7.8 Hz, 2H), 2.60 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (63 MHz, DMSO) δ 169.8, 154.9, 153.9, 146.7, 138.8, 138.5, 135.5, 130.7, 129.3, 128.3, 126.7, 117.7, 22.6, 20.9; IR (KBr) ν 3380, 3204, 2913, 1692, 1651, 1620, 1584, 1546, 1359, 822, 761, 700 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{18}N_2O$ C 79.44, H 6.00, N 9.26; found C 79.24, H 5.95, N 9.30.

4,6-Bis(4-methylphenyl)-2-methylnicotinamide (3c): White solid; mp 247−249 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.94 (d, J = 8.2 Hz, 2H), 7.55 (s, 1H), 7.47 (d, J = 8.1 Hz, 2H), 7.37−7.19 (m, J = 7.9, 3.0 Hz, 4H), 5.69 (bs, 1H), 5.44 (bs, 1H), 2.76 (s, 3H), 2.44 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.1, 157.2, 155.7, 147.5, 139.4, 138.9, 136.1, 135.4, 129.7, 129.6, 128.6, 128.2, 127.1, 118.3, 23.0, 21.4, 21.4; IR (KBr) ν 3446, 3289, 3180, 1652, 1606, 1540, 1512, 1360, 1189, 825, 795, 582, 572, 542 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{20}N_2O$ C 79.72, H 6.37, N 8.85; found C 79.81, H 6.26, N 8.62.

4-(4-Methoxyphenyl)-2-methyl-6-phenylnicotinamide (3d): White solid; mp 233−235 °C; ^{1}H NMR (250 MHz, DMSO) δ = 8.14 (dd, J = 7.8, 1.5 Hz, 2H), 7.88 (s, 1H), 7.72 (s, 1H), 7.63−7.40 (m, 6H), 7.05 (d, J = 8.7 Hz, 2H), 3.82 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (63 MHz, DMSO) δ 170.0, 159.5, 154.8, 154.0, 146.3, 138.4, 130.9, 130.5, 129.7, 129.1, 128.7, 126.8, 117.9, 113.8, 55.2, 22.6; IR (KBr) ν 3373, 3195, 2840, 1682, 1652, 1644, 1608, 1586, 1574, 1515, 832, 767, 697 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{18}N_2O_2$ C 75.45, H 5.70, N 8.80; found C 75.11, H 5.64, N 8.71.

4,6-Bis(4-methoxyphenyl)-2-methylnicotinamide (3e): Pale yellow solid; mp 239−241 °C; ^{1}H NMR (250 MHz, DMSO) δ = 8.11 (d, J = 8.6 Hz, 2H), 7.84 (s, 1H), 7.65 (s, 1H), 7.58 (d, J = 8.6 Hz, 2H), 7.53 (s, 1H), 7.04 (d, J = 7.4 Hz, 4H), 3.83 (s, 3H), 3.82 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (63 MHz, DMSO) δ 170.1, 160.2, 159.5, 154.5, 153.8, 146.3, 130.8, 130.7, 130.2, 129.7, 128.1, 117.0, 114.1, 113.8, 55.2, 55.2, 22.6; IR (KBr) ν 3363, 3188, 2970, 1836, 1683, 1644, 1607, 1513, 1463, 1361, 1296, 1260, 1175, 1032, 829 cm^{-1}; elemental

dx.doi.org/10.1021/co300081k | ACS Comb. Sci. 2012, 14, 551−557

analysis calcd (%) for $C_{21}H_{20}N_2O_3$ C 72.40, H 5.79, N 8.04; found C 72.11, H 5.74, N 7.90.

4,6-Bis(4-chlorophenyl)-2-methylnicotinamide (3f): White solid; mp 259−261 °C; ^{1}H NMR (250 MHz, DMSO) δ = 8.21 (d, J = 8.6 Hz, 2H), 7.93 (s, 1H), 7.82 (s, 1H), 7.68−7.51 (m, 7H), 2.61 (s, 3H); ^{13}C NMR (63 MHz, DMSO) δ 169.4, 154.3, 153.7, 145.7, 137.0, 136.9, 134.1, 133.5, 131.2, 130.3, 128.7, 128.6, 128.4, 118.0, 22.5; IR (KBr) ν 3314, 3157, 1668, 1600, 1543, 1493, 1366, 1091, 1015, 829, 673 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{14}Cl_2N_2O$ C 63.88, H 3.95, N 7.84; found C 63.54, H 3.94, N 7.88.

6-(4-Chlorophenyl)-2-methyl-4-(2-nitrophenyl)-nicotinamide (3g): Pale yellow solid; mp 228−230 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 8.07 (d, J = 7.3 Hz, 1H), 7.94 (d, J = 8.5 Hz, 2H), 7.78−7.58 (m, 2H), 7.50−7.40 (m, 3H), 7.29 (s, 1H), 6.08 (s, 1H), 5.76 (s, 1H), 2.78 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.6, 156.1, 155.9, 148.2, 144.5, 136.7, 135.8, 133.5, 133.1, 131.7, 129.9, 129.1, 128.9, 128.5, 124.5, 116.5, 23.0; IR (KBr) ν 3443, 3122, 1682, 1652, 1584, 1574, 1557, 1520, 1506, 1495, 1360, 1094, 840, 784, 735, 700, 531 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{14}ClN_3O_3$ C 62.05, H 3.84, N 11.43; found C 61.95, H 3.87, N 11.24.

2-Methyl-4-(4-methylphenyl)-6-(2-nitrophenyl)-nicotinamide (3h): White solid; mp 214−216 °C; ^{1}H NMR (250 MHz, DMSO) δ = 8.07−7.88 (m, 3H), 7.85−7.76 (m, 1H), 7.75−7.66 (m, 1H), 7.64 (s, 1H), 7.59 (s, 1H), 7.55 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 2.49 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (63 MHz, DMSO) δ 169.4, 154.0, 153.3, 149.2, 146.8, 138.1, 134.9, 133.5, 132.7, 131.4, 131.3, 129.9, 129.1, 128.3, 124.2, 120.3, 22.2, 20.8; IR (KBr) ν 3370, 3188, 1667, 1585, 1538, 1434, 1360, 1115, 1090, 824, 782, 753, 710 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{17}N_3O_3$ C 69.15, H 4.93, N 12.10; found C 68.95, H 4.95, N 12.11.

2,5-Dimethyl-4,6-diphenylnicotinamide (3i): White solid; mp 228−230 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.58−7.38 (m, 8H), 7.32 (dd, J = 7.5, 1.8 Hz, 2H), 5.53 (s, 1H), 5.37 (s, 1H), 2.69 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.4, 159.4, 151.6, 147.8, 140.7, 137.4, 130.3, 129.1, 128.7, 128.6, 128.4, 128.3, 128.2, 126.4, 22.5, 17.8; IR (KBr) ν 3346, 3175, 3055, 2923, 1668, 1652, 1614, 1557, 1493, 1444, 1402, 1360, 751, 701 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{18}N_2O$ C 79.44, H 6.00, N 9.26; found C 79.25, H 6.07, N 9.16.

***N*-Cyclohexyl-4,6-bis(4-methylphenyl)-2-methylnicotinamide (3j):** Pale yellow solid; mp 214−216 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.93 (d, J = 8.2 Hz, 2H), 7.54 (s, 1H), 7.44 (d, J = 8.1 Hz, 2H), 7.37−7.18 (m, 4H), 5.25 (d, J = 8.5 Hz, 1H), 3.94−3.74 (m, 1H), 2.73 (s, 3H), 2.43 (s, 6H), 1.74−1.47 (m, 5H), 1.41−1.21 (m, 2H), 1.17−1.03 (m, 1H), 0.97−0.78 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.9, 157.0, 155.9, 147.6, 139.3, 138.7, 136.3, 135.5, 129.8, 129.6, 129.4, 128.2, 127.1, 118.2, 48.2, 32.5, 25.4, 24.6, 23.0, 21.4, 21.3; IR (KBr) ν 3230, 3062, 2922, 2851, 1620, 1325, 1260, 1186, 1151, 1113, 1020, 860, 819, 725, 712 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{30}N_2O$ C 81.37, H 7.59, N 7.03; found C 81.12, H 7.32, N 6.98.

2-Methyl-*N*,4,6-triphenylnicotinamide (3k): Pale yellow solid; mp 226−228 °C; ^{1}H NMR (250 MHz, DMSO) δ = 10.50 (s, 1H), 8.20 (d, J = 6.5 Hz, 2H), 7.86 (s, 1H), 7.64 (d, J = 6.5 Hz, 2H), 7.59−7.38 (m, 8H), 7.30 (t, J = 7.8 Hz, 3H), 7.08 (t, J = 7.2 Hz, 1H), 2.64 (s, 3H); ^{13}C NMR (63 MHz, DMSO) δ 166.3, 155.6, 154.5, 147.4, 138.6, 138.2, 138.0, 130.5, 129.4, 128.8, 128.7, 128.6, 128.5, 128.2, 126.9, 123.9, 119.7, 118.2, 22.6; IR (KBr) ν 3270, 3063, 1649, 1602, 1546, 1489, 1442, 1373, 1326, 1239, 886, 759, 693 cm^{-1}; elemental analysis calcd (%) for $C_{25}H_{20}N_2O$ C 82.39, H 5.53, N 7.69; found C 82.14, H 5.61, N 7.57.

2-Ethyl-N,4,6-triphenylnicotinamide (3l): White solid; mp 232−234 °C; ^{1}H NMR (250 MHz, DMSO) δ = 10.46 (s, 1H), 8.21 (dd, J = 7.9, 1.5 Hz, 2H), 7.85 (s, 1H), 7.63 (dd, J = 7.9, 1.5 Hz, 2H), 7.58−7.36 (m, 8H), 7.28 (t, J = 7.8, 2H), 7.06 (t, J = 7.3, 1H), 2.91 (q, J = 7.5 Hz, 2H), 1.36 (t, J = 7.5 Hz, 3H); ^{13}C NMR (63 MHz, DMSO) δ 166.3, 159.0, 155.6, 147.4, 138.6, 138.3, 138.1, 130.2, 129.3, 128.8, 128.8, 128.5, 128.3, 126.9, 123.9, 119.6, 118.2, 28.6, 13.7; IR (KBr) ν 3265, 3128, 3017, 2973, 1652, 1538, 1369, 1323, 1240, 1184, 1142, 1104, 1074, 758, 692, 566 cm^{-1}; elemental analysis calcd (%) for $C_{26}H_{22}N_2O$ C 82.51, H 5.86, N 7.40; found C 82.23, H 5.89, N 7.56.

***N*,4,6-Triphenyl-2-propylnicotinamide (3m):** White solid; mp 230−232 °C; ^{1}H NMR (250 MHz, DMSO) δ = 10.42 (s, 1H), 8.20 (dd, J = 7.9, 1.4 Hz, 2H), 7.84 (s, 1H), 7.63 (dd, J = 7.9, 1.5 Hz, 2H), 7.56−7.36 (m, 8H), 7.28 (t, J = 7.8 Hz, 2H), 7.06 (t, J = 7.3 Hz, 1H), 2.90−2.80 (m, 2H), 1.96−1.76 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (63 MHz, DMSO) δ 166.3, 157.9, 155.5, 147.4, 138.5, 138.4, 138.1, 130.5, 129.3, 128.8, 128.8, 128.5, 128.5, 128.3, 126.9, 123.9, 119.7, 118.2, 37.4, 22.2, 14.1; IR (KBr) ν 3230, 3130, 3062, 2955, 2925, 2869, 1645, 1600, 1538, 1488, 1443, 1376, 1328, 888, 765, 740, 702, 692 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{24}N_2O$ C 82.62, H 6.16, N 7.14; found C 82.36, H 6.09, N 7.00.

2-Isopropyl-*N*,4,6-triphenylnicotinamide (3n): White solid; mp 252−254 °C; ^{1}H NMR (250 MHz, DMSO) δ = 10.44 (s, 1H), 8.22 (d, J = 6.8 Hz, 2H), 7.83 (s, 1H), 7.64 (d, J = 6.7 Hz, 2H), 7.57−7.34 (m, 8H), 7.27 (t, J = 7.7 Hz, 2H), 7.05 (t, J = 7.1 Hz, 1H), 3.36−3.11 (m, 1H), 1.36 (d, J = 6.5, 6H); ^{13}C NMR (63 MHz, DMSO) δ 166.3, 162.4, 155.6, 147.3, 138.5, 138.5, 138.2, 129.7, 129.3, 128.8, 128.7, 128.4, 128.3, 126.8, 123.8, 119.7, 118.2, 32.7, 22.6; IR (KBr) ν 3230, 3130, 3062, 2970, 2926, 1646, 1599, 1588, 1552, 1538, 1496, 1443, 1336, 888, 771, 758, 704, 691 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{24}N_2O$ C 82.62, H 6.16, N 7.14; found C 82.41, H 6.22, N 7.05.

(2-Methyl-4,6-diphenylpyridin-3-ylcarbonyl)-(piperidin-1-yl)ketone (3o): Pale yellow solid; mp 212−214 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 8.15−7.96 (m, 2H), 7.71−7.55 (m, 3H), 7.55−7.41 (m, 6H), 3.74−3.58 (m, 1H), 3.58−3.42 (m, 1H), 3.07−2.92 (m, 1H), 2.86−2.72 (m, 1H), 2.68 (s, 3H), 1.60−1.35 (m, 3H), 1.35−1.14 (m, 2H), 0.80−0.58 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.7, 156.9, 155.3, 146.9, 139.0, 138.1, 129.1, 128.8, 128.7, 128.6, 127.1, 118.2, 47.2, 42.1, 25.8, 25.1, 24.2, 22.9; IR (KBr) ν 3438, 3058, 2940, 2858, 1628, 1586, 1545, 1494, 1443, 1369, 1272, 1237, 1000, 788, 765, 743, 701 cm^{-1}; elemental analysis calcd (%) for $C_{24}H_{24}N_2O$ C 80.87, H 6.79, N 7.86; found C 80.58, H 6.70, N 7.59.

(2-Methyl-4,6-diphenylpyridin-3-ylcarbonyl)-(morpholin-4-yl)ketone (3p): Pale yellow solid; mp 132−134 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 8.11−8.00 (m, 2H), 7.64 (s, 1H), 7.62−7.45 (m, 8H), 3.80−3.49 (m, 3H), 3.41−3.22 (m, 1H), 3.17−3.01 (m, 1H), 2.91−2.75 (m, 1H), 2.70 (s, 3H), 2.68−2.56 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 168.0, 157.4, 155.6, 147.2, 138.8, 138.0, 129.4, 129.2, 129.0, 128.9, 128.6, 127.8, 127.2, 118.1, 66.3, 66.3, 46.6, 41.7, 23.0; IR (KBr) ν 3052, 2983, 2918, 2859, 1634, 1587, 1540, 1495, 1436, 1383,

dx.doi.org/10.1021/co300081k | *ACS Comb. Sci.* 2012, 14, 551−557

1366, 1302, 1277, 1260, 1238, 1113, 1008, 788 cm^{-1}; elemental analysis calcd (%) for $C_{23}H_{22}N_2O_2$ C 77.07, H 6.19, N 7.82; found C 76.91, H 6.24, N 7.80.

(2-Methyl-4,6-diphenylpyridin-3-ylcarbonyl)(4-methylpiperazin-1-yl)ketone (3q): Yellow solid; mp 132−134 °C; ^1H NMR (250 MHz, $CDCl_3$) δ = 8.06 (dd, J = 8.0 Hz, 1.6, 2H), 7.63 (s, 1H), 7.61−7.45 (m, 8H), 3.81−3.52 (m, 2H), 3.22−3.01 (m, 1H), 2.91−2.75 (m, 1H), 2.69 (s, 3H), 2.49−2.32 (m, 1H), 2.15 (s, 3H), 2.19−1.99 (m, 2H), 1.52−1.37 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.9, 157.2, 155.5, 147.1, 139.0, 138.1, 129.3, 129.0, 128.9 (two signals), 128.7, 128.2, 127.1, 118.1, 54.5, 54.2, 46.0, 45.9, 41.1, 23.0; IR (KBr) ν 3445, 3052, 2997, 2938, 2844, 2796, 1620, 1574, 1541, 1441, 1294, 1271, 1018, 999, 760, 700 cm^{-1}; elemental analysis calcd (%) for $C_{24}H_{25}N_3O$ C 77.60, H 6.78, N 11.31; found C 77.44, H 6.67, N 11.02.

2-Methyl-6-phenyl-4-(thiophen-2-yl)nicotinamide (3r): Pale yellow solid, mp 199−201 °C; ^1H NMR (250 MHz, $CDCl_3$) δ = 8.03 (dd, J = 8.0, 1.7 Hz, 2H), 7.68 (s, 1H), 7.58−7.42 (m, 5H), 7.16 (dd, J = 5.1, 3.7 Hz, 1H), 5.86 (bs, 1H), 5.71 (bs, 1H), 2.77 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.1, 157.5, 155.8, 139.9, 138.9, 138.6, 129.5, 128.9, 128.5, 128.3, 128.0, 127.8, 127.2, 118.1, 22.9; IR (KBr) ν 3310, 3140, 1652, 1591, 1495, 1433, 1376, 1242, 1094, 856, 767, 677, 622 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{14}N_2OS$ C 69.36, H 4.79, N 9.52, S 10.89; found C 68.99, H 4.92, N 9.42, S 10.85.

2-Methyl-6-(4-methylphenyl)-4-(thiophen-2-yl)-nicotinamide (3s): Pale yellow solid; mp 206−208 °C; ^1H NMR (250 MHz, $CDCl_3$) δ = 7.94 (d, J = 8.2 Hz, 2H), 7.65 (s, 1H), 7.53 (dd, J = 3.6, 0.9 Hz, 1H), 7.48 (dd, J = 5.1, 0.9 Hz, 1H), 7.32 (d, J = 8.2 Hz, 2H), 7.16 (dd, J = 5.1, 3.6 Hz, 1H), 5.79 (s, 1H), 5.73 (s, 1H), 2.76 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.1, 157.5, 155.7, 139.9, 139.7, 139.0, 135.8, 129.6, 128.5, 128.2, 127.7, 127.1, 117.8, 22.9, 21.4; IR (KBr) ν 3438, 3278, 3169, 1651, 1545, 1513, 1431, 1357, 829, 703, 556, 538 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{16}N_2OS$ C 70.10, H 5.23, N 9.08, S 10.40; found C 69.88, H 5.30, N 8.98, S 10.33.

2-Methyl-6-phenyl-4-styrylnicotinamide (3t): Pale yellow solid; mp 199−201 °C; ^1H NMR (250 MHz, DMSO) δ = 8.27−8.09 (m, 4H), 7.91−7.72 (m, 2H), 7.66−7.32 (m, 8H), 7.15 (d, J = 16.3 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR (63 MHz, DMSO) δ 169.7, 154.8, 154.0, 141.6, 138.5, 136.3, 134.2, 130.9, 129.1, 129.0, 128.8, 128.7, 126.9, 126.8, 123.4, 112.6, 22.5; IR (KBr) ν 3380, 3180, 1640, 1576, 1540, 1496, 1448, 1385, 1269, 1217, 1121, 958, 767, 690 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{18}N_2O$ C 80.23, H 5.77, N 8.91; found C 79.90, H 5.79, N 8.82.

2-Methyl-6-phenyl-4-(1-phenylprop-1-en-2-yl)-nicotinamide (3u): White solid, mp 186−188 °C; ^1H NMR (250 MHz, DMSO) δ = 8.14 (dd, J = 8.0, 1.5 Hz, 2H), 7.92 (s, 1H), 7.77 (s, 1H), 7.66 (s, 1H), 7.57−7.23 (m, 8H), 6.65 (s, 1H), 2.59 (s, 3H), 2.25 (d, J = 1.2 Hz, 3H); ^{13}C NMR (63 MHz, DMSO) δ 169.9, 154.6, 154.0, 150.9, 138.3, 137.0, 135.4, 130.5, 129.8, 129.1, 128.9, 128.7, 128.3, 127.0, 126.7, 116.4, 22.7, 18.7; IR (KBr) ν 3398, 3312, 3201, 3059, 1689, 1651, 1620, 1586, 1576, 1537, 1358, 1154, 1076, 1005, 755, 700 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{20}N_2O$ C 80.46, H 6.14, N 8.53; found C 80.14, H 6.07, N 8.65.

2-Oxo-4,6-Diphenylcyclohex-3-enecarboxamide (5) from Robinson Annelation: Pale yellow solid; mp 175−177 °C; ^1H NMR (250 MHz, $CDCl_3$) ^1H NMR (250 MHz, $CDCl_3$) δ = 7.59 (dd, J = 6.7, 3.0, 2H), 7.52 − 7.42 (m, 3H), 7.41−7.32 (m, 5H), 6.60 (s, 1H), 5.97 (bs, 1H), 5.43 (bs, 1H), 4.10 (td, J = 8.8, 5.2, 1H), 3.62 (d, J = 8.9, 1H), 3.33 (dd, J = 18.0, 5.0, 1H), 3.06 (dd, J = 18.0, 9.0, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 196.0, 170.9, 159.9, 142.3, 138.2, 130.9, 129.3, 129.2, 127.8, 127.6, 126.7, 124.6, 59.1, 42.8, 35.3; IR (KBr) ν 3049, 1679, 1650, 1599, 1543, 1367, 1112, 758 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{17}NO_2$ C 78.33; H 5.88; N 4.81; found C 78.60, H 5.96, N 4.97.

***tert*-Butyl 5-oxo-2,4-diphenyl-4,5,7,8-tetrahydro-1,6-naphthyridine-6(1*H*)-carboxylate (7a):** White solid; mp 253 °C (dec.); ^1H NMR (250 MHz, DMSO) δ = 8.79 (s, 1H), 7.53−7.45 (m, 2H), 7.45−7.34 (m, 3H), 7.31−7.26 (m, 4H), 7.21−7.09 (m, 1H), 5.21 (dd, J = 5.3, 1.6 Hz, 1H), 4.63 (d, J = 5.4 Hz, 1H), 4.08−3.94 (m, 1H), 3.56−3.39 (m, 1H), 2.82−2.57 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (63 MHz, DMSO) δ 164.6, 152.5, 149.5, 148.2, 134.9, 134.2, 128.5, 128.4, 128.2, 127.4, 125.8, 125.5, 105.1, 99.5, 80.8, 42.0, 37.9, 27.8, 26.3; IR (KBr) ν 3324, 3058, 3022, 2975, 2930, 2879, 1748, 1656, 1620, 1504, 1402, 1369, 1310, 1217, 1158, 1130, 914, 757, 697 cm^{-1}; elemental analysis calcd (%) for $C_{25}H_{26}N_2O_3$ C 74.60, H 6.51, N 6.96; found C 74.70, H 6.42, N 7.08.

2,4-Diphenyl-4,6,7,8-tetrahydro-1,6-naphthyridin-5(1*H*)-one (7b): Pale yellow solid; mp 267−269 °C; ^1H NMR (250 MHz, DMSO) δ = 8.27 (s, 1H), 7.48 (dd, J = 8.0, 1.7 Hz, 2H), 7.42−7.31 (m, 3H), 7.25 (d, J = 4.3 Hz, 4H), 7.18−7.04 (m, 1H), 6.77 (s, 1H), 5.09 (dd, J = 5.3, 1.6 Hz, 1H), 4.61 (d, J = 5.3 Hz, 1H), 3.29−3.09 (m, 2H), 2.59−2.50 (m, 2H); ^{13}C NMR (63 MHz, DMSO) δ 168.1, 148.9, 145.5, 135.5, 135.0, 128.4, 128.2, 128.1, 127.6, 127.5, 125.5, 125.4, 103.6, 99.4, 37.8, 37.45 26.3; IR (KBr) ν 3395, 3227, 3116, 2992, 2900, 1660, 1652, 1634, 1614, 1514, 1505, 1495, 1470, 1434, 1417, 1385, 1332, 1282, 1230, 1199, 1032, 757, 697 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{18}N_2O$ C 79.44, H 6.00, N 9.26; found C 79.54, H 5.80, N 8.99.

2,4-Diphenyl-7,8-dihydro-1,6-naphthyridin-5(6*H*)-one (8b): Pale yellow solid; mp 236−238 °C; ^1H NMR (250 MHz, DMSO) δ = 8.23−8.11 (m, 2H), 8.05 (s, 1H), 7.72 (s, 1H), 7.55−7.45 (m, 3H), 7.40 (s, 5H), 3.57−3.43 (m, 2H), 3.13 (t, J = 6.0, 2H); ^{13}C NMR (63 MHz, DMSO) δ 163.5, 160.8, 156.6, 151.3, 139.9, 137.7, 129.8, 128.8, 128.5, 127.6, 127.1, 121.9, 121.1, 37.9, 32.7; IR (KBr) ν 2887, 1668, 1652, 1574, 1538, 1480, 14034, 1344, 1247, 1171, 1078, 824, 761, 698 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{16}N_2O$ C 79.98, H 5.37, N 9.33; found C 79.95, H 5.54, N 9.14.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Javier Blázquez for some experimental assistance. Financial support from MICINN (grant CTQ2009-12320-BQU) and Universidad Complutense (grant GR35/10-A-920234 and fellowship to G.T.) is also gratefully acknowledged.

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