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Synthesis of Substituted Phthalimides *via* Ultrasound-Promoted One-Pot Multicomponent Reaction

Abdolali Alizadeh,* Behnaz Farajpour, Tim-Oliver Knedel, and Christoph Janiak

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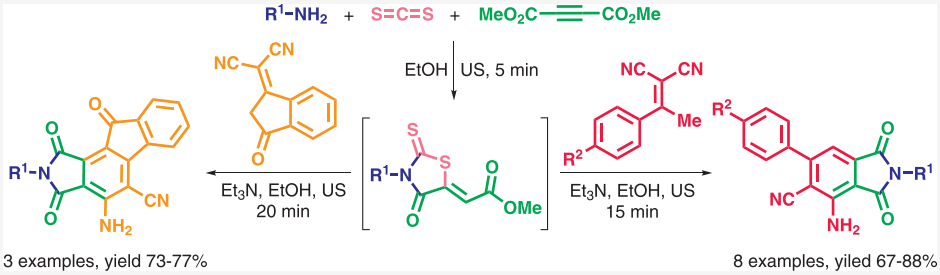

ABSTRACT: In this work, a novel strategy for the straightforward synthesis of substituted phthalimides is described, which includes base-mediated Michael addition/intramolecular cyclization/[1,5]-*H* shift/cleavage of CS_2/aromatization/nucleophilic acyl substitution reaction of 2-(4-oxo-2-thioxothiazolidin-5-ylidene)acetates and *α*,*α*-dicyanoolefines under ultrasound (US) irradiation. Some advantages of this method are as follows: having simple operation, easily accessible starting materials, chemoselective cascade process, synthetically useful yields, and green conditions by utilizing US irradiation as a source of energy and using ethanol as solvent.

INTRODUCTION

One of the primary goals of organic and medicinal chemistry is the design and synthesis of scaffolds possessing biological features. Phthalimide core,[1−4] in particular, serves as the structural unit in various drugs such as thalidomide,[5,6] pomalidomide,[7] apremilast,[8] and batracylin[9] (Figure 1). Furthermore, phthalimides have been used as intermediates to produce functionalized natural products and alkaloids, including nuevamine,[10] chilenine,[11] lennoxamine,[12] and magallanesine.[13] These naturally occurring molecules and their analogues are promising anti-cancer, anti-microbial, anti-inflammatory, and anti-leukemic agents.

Increasing attention has been paid to the synthesis of phthalimide derivatives because of their existence in numerous biologically active molecules.[14] For instance, Jiang and co-workers reported palladium-catalyzed reaction of isocyanides and bromoacetylenes toward the synthesis of phthalimides *via* double insertion of isocyanides.[15] Microwave-assisted solid-phase synthesis of phthalimides *via* utilizing anchored phthalic acid and amines has been disclosed by Chassaing et al.[16] Biu and co-workers utilized fluoride promoted reaction of arynes, isocyanides, and CO_2 to yield phthalimides.[17]

Also, copper-catalyzed cycloaddition reactions of oximes and maleimides gave fused-phthalimides.[18] Interestingly, Abdelhamid and co-workers demonstrated a straightforward protocol to obtain phthalimide derivatives.[19] Despite the importance of the existing developed protocols, most of these methods use expensive prefunctionalized starting materials and reagents,

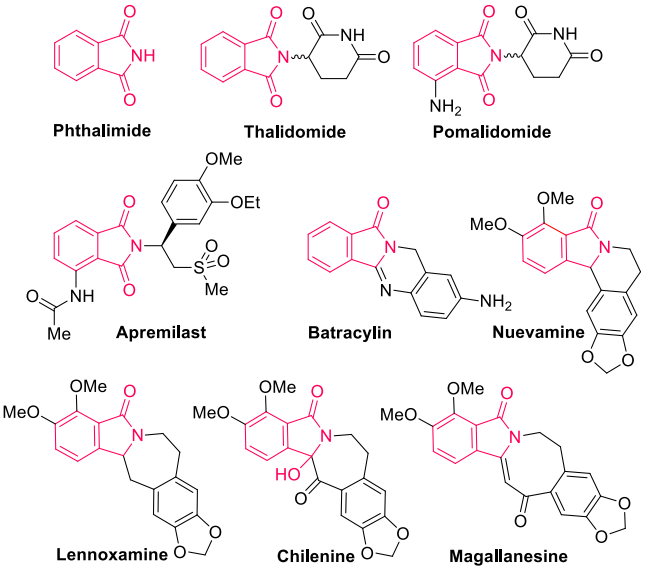

Figure 1. Structure of phthalimide and some chemical compounds possessing this substructure.

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transition-metals, or specific conditions. Therefore, the development of simple and potent strategies for the synthesis of such compounds *via* readily available starting materials is still worth exploring and is highly desirable.

Herein, we wish to report the synthesis of substituted phthalimides using an ultrasound (US)-assisted cascade reaction of 2-(4-oxo-2-thioxothiazolidin-5-ylidene)acetates[20] and α,α-dicyanoolefines.[21]

It should be mentioned that US irradiation is a clean and efficient energy source for organic transformations, especially in the field of multicomponent reactions.[22] The sonochemistry has several benefits such as enhancement of reaction rates, having lower costs, minimizing the side products, having more selectivity, and affording excellent yields that have led to widespread applications in many organic synthesis processes.[23−25] Moreover, 2-(4-oxo-2-thioxothiazolidin-5-ylidene)-acetates are unique starting materials for the diversity-oriented synthesis of chemical compounds, and they have been employed as electrophilic C2 synthons in several formal [2 + 3] and [2 + 4] cycloaddition reactions.[26] Indeed, we reasoned that from the formal [4 + 2] annulation of starting materials, a spiro intermediate could be produced,[27,28] which after tandem CS_2 cleavage/aromatization/nucleophilic acyl substitution could be transformed to phthalimide derivatives. As far as we know, this is the only report that considers all potential active sites of 2-(4-oxo-2-thioxothiazolidin-5-ylidene)acetates to participate in an US-assisted cascade reaction (Figure 2).

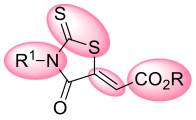

Figure 2. Plausible active sites of α,β-unsaturated rhodanines.

RESULTS AND DISCUSSION

Initially, we commenced our exploration with the synthesis of 2-(1-phenylethylidene)malononitrile **5a** as a multifunctional synthon *via* the Knoevenagel condensation of acetophenone and malononitrile.[29] On the other hand, the US-mediated reaction of benzylamine, CS_2, and dimethyl acetylendicarboxylate was conducted in EtOH to afford methyl 2-(3-benzyl-4-oxo-2-thioxothiazolidin-5-ylidene)acetate **4a**.[19] Then, without further purification within a one-pot sequential process, the prepared 2-(1-phenylethylidene)malononitrile **5a** and piperidine were added to the reaction mixture under ultrasonic irradiation with an amplitude of 60%. To our delight, 4-amino-2-benzyl-1,3-dioxo-6-phenylisoindoline-5-carbonitrile **6a** was obtained in 67% yield within 30 min (Scheme 1). The structure of **6a** was identified by its IR, mass, elemental analysis, ^{1}H NMR, and ^{13}C NMR spectra.

Inspired by this initial result, the one-pot sequential reaction of 2-(3-benzyl-4-oxo-2-thioxothiazolidin-5-ylidene)acetate **4a** and 2-(1-phenylethylidene)malononitrile **5a** was selected as the model reaction, then the effect of different amplitudes of US irradiation (20, 40, 60, and 80%) on the reaction was explored. The best reaction yield and the shorter reaction time were obtained under US irradiation with an amplitude of 60% (Table 1, entry 3). Although lower amplitudes (20 and 40%) did not significantly influence the reaction yield, they affected the time of the reaction (Table 1, entry 1 and 2). Moreover, the reaction was carried out under US irradiation with 80% of amplitude in 10 min, but product **6a** was obtained in lower yields (Table 1, entry 4). Next, for investigating the influence of the base on the reaction outcome, various bases were examined. The results revealed that 1.0 equiv of Et_3N is more efficient than other bases, delivering **6a** in 78% yield (Table 1, entry 3).

Although the reaction proceeded faster in the presence of inorganic bases, more side products were observed which influenced the yield of the desired product. Furthermore, screening of solvents such as EtOH, H_2O, dimethylformamide (DMF), MeCN, tetrahydrofuran (THF), and dichloromethane (DCM) showed that EtOH is the best solvent for this reaction. Additionally, the possibility of the reaction was examined under the reflux of EtOH instead of ultrasonic irradiation in the presence of Et_3N to yield **6a** in 74% within 2 h (Table 1). Notably, the desired product was not formed at ambient temperature after 24 h.

Having optimized reaction conditions in hand, the generality and substrate scope for this one-pot sequential four-component process were evaluated (Scheme 2).

Initially, the reaction of different substituted α,α-dicyanoolefins (**5a**−**5g**) with **4a** was examined. The reaction yield in the presence of electron-withdrawing substituents such as Cl and Br (73−88%) was better than electron-donating substituents such as Me and OMe (73−76%). Notably, the reaction did not proceed well in the presence of the nitro group as a strong electron-withdrawing substituent. Products **6f**−**6h** can be obtained from 4-methylbenzylamine or allylamine as alternative amines (Scheme 2). We then switched our investigation to the reaction of 2-(3-oxo-2,3-dihydro-1*H*-inden-1-ylidene)-malononitrile **5′** instead of **5**. Gratifyingly, its reaction was well tolerated to deliver **6a′** in 75% yield within 20 min. Furthermore, the allyl and butylamine worked well in this cascade reaction which gave the corresponding fused-phthalimides **6b′** and **6c′** (Scheme 2). The molecular structures of all synthesized compounds were characterized by Fourier transform infrared (FTIR), mass spectrometry, elemental analysis, and NMR. Also, the structure of **6a′** was confirmed by single-crystal X-ray crystallographic analysis.

The mechanism of the first step including 2-(4-oxo-2-thioxothiazolidin-5-ylidene)acetates formation is known.[19,22] A possible mechanism for the second step which leads to 4-amino-

Scheme 1. One-Pot Sequential Synthesis of 6a under Ultrasound Irradiation

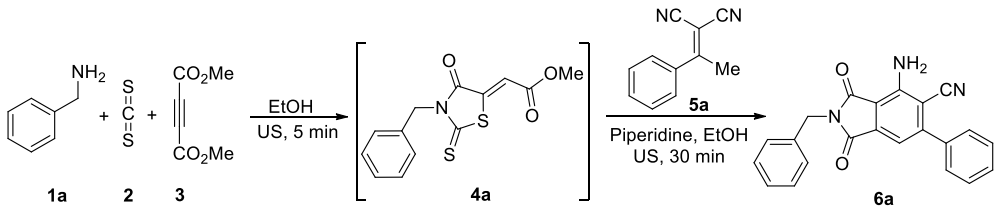

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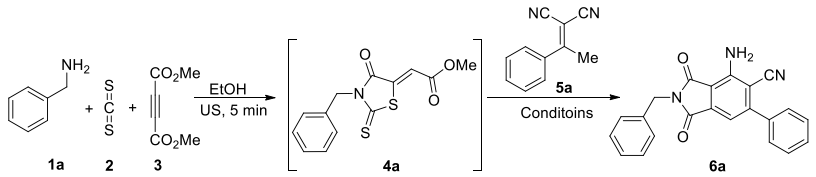
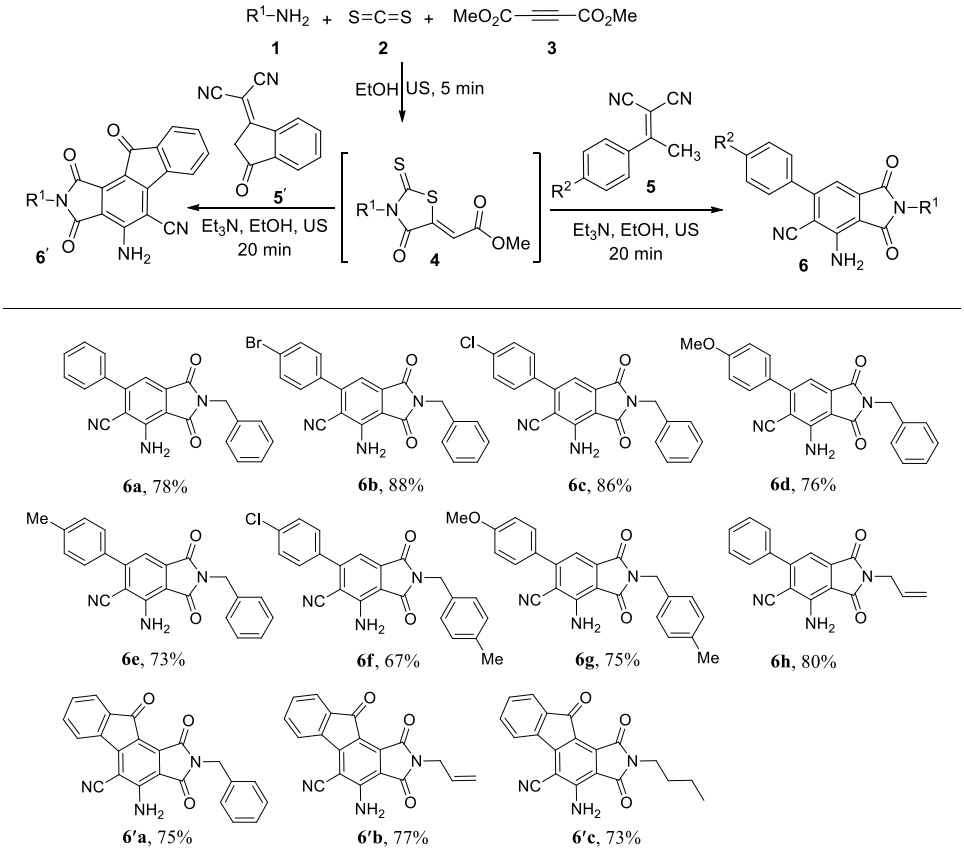
Table 1. Survey on Conditions for the Synthesis of 6a[a]



entry	base	solvent	method	time (min)	yield (%)
1[b]	Et_3N	EtOH	US	30	71
2[c]	Et_3N	EtOH	US	25	74
3[d,g]	Et_3N	EtOH	US	15	78
4[e]	Et_3N	EtOH	US	10	62
5[d]	Et_3N	H_2O	US	20	68
6[d]	Et_3N	DMF	US	15	69
7[d]	Et_3N	MeCN	US	25	65
8[d]	Et_3N	THF	US	70	35
9[d]	Et_3N	DCM	US	55	43
10[d]	Piperidine	EtOH	US	30	67
11[d]	Pyridine	EtOH	US	90	20
12[d]	K_2CO_3	EtOH	US	20	59
13[d]	KOH	EtOH	US	10	61
14[f]	Et_3N	EtOH	Reflux	120	74

[a]To a mixture of benzylamine (107 mg, 1.0 mmol) and carbon disulfide (115 mg, 1.5 mmol) in solvent (5 mL), DMAD (142 mg, 1.0 mmol) was added. Then, the mixture was subjected to US irradiation (20 kHz). The reaction was completed within 5 min, then α,α-dicyanoolefine **5a** (168 mg, 1.0 mmol) and base (1.0 mmol) were added. The reaction was performed under ultrasonic irradiation, and its progress was followed by TLC until the total consumption of the starting materials. [b]Reaction carried out under US irradiation (20% of amplitude). [c]Reaction carried out under US irradiation (40% of amplitude). [d]Reaction carried out under US irradiation (60% of amplitude). [e]Reaction carried out under US irradiation (80% of amplitude). [f]Reaction carried out under reflux conditions. [g]Final temperature of the reaction was 51 °C.

Scheme 2. Synthesis of Novel Substituted Phthalimides



2-benzyl-1,3-dioxo-6-phenylisoindoline-5-carbonitrile **6a** is depicted in Scheme 3.

Initially, Et_3N deprotonates **5a** to give intermediate **7a**. Intermediate **7a** then undergoes Michael addition with

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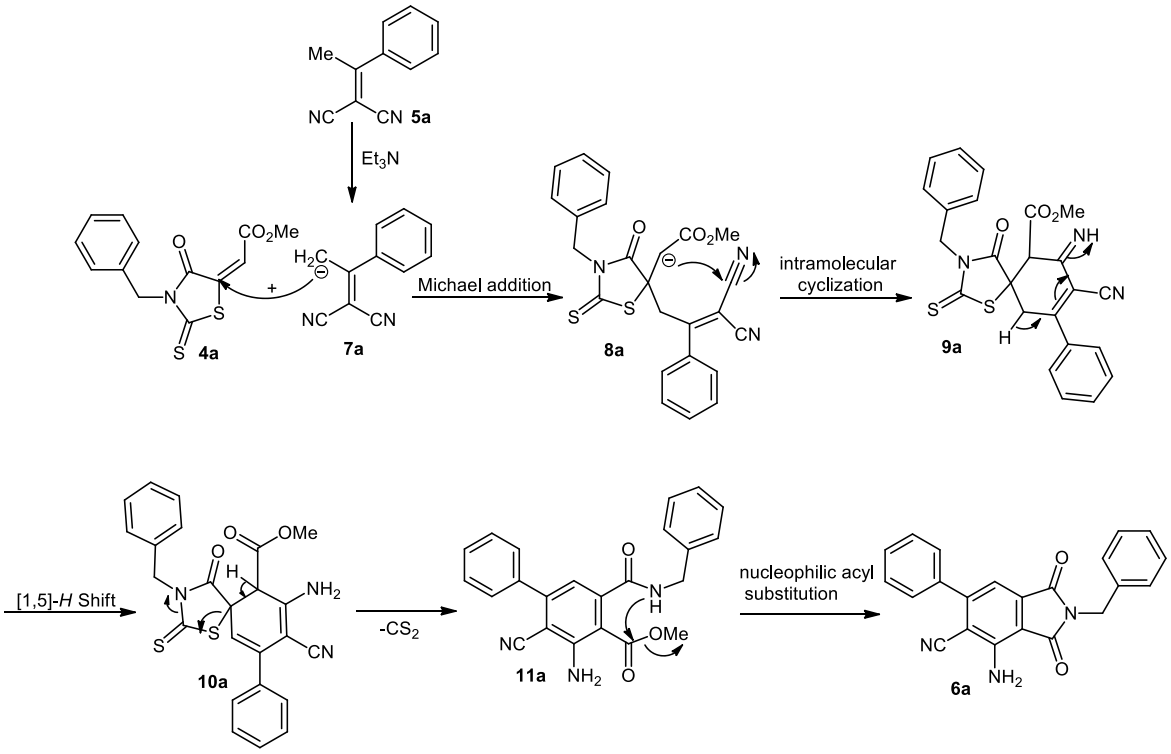
Scheme 3. Proposed Mechanism for the Formation of 6a



compound **4a** to generate intermediate **8a**. In the next steps, intramolecular cyclization and subsequent [1,5]-*H* shift happen to form intermediate **10a**. Aromatic intermediate **11a** is obtained after elimination of CS_2 from intermediate **10a**. Finally, ring closing of the amide nitrogen with the ester group leads to product **6a**.

CONCLUSIONS

In summary, the US-mediated cascade reaction of 2-(4-oxo-2-thioxothiazolidin-5-ylidene)acetates and α,α-dicyanoolefines was described, allowing the chemoselective synthesis of substituted phthalimides in satisfactory yields. These transformations include the domino-style formation of C−C/C−C/C−N bonds through Michael addition/intramolecular cyclization/[1,5]-*H* shift/cleavage of CS_2/aromatization/nucleophilic acyl substitution. It is noteworthy that 2-(4-oxo-2-thioxothiazolidin-5-ylidene)acetates could either be synthesized prior to the reaction or generated *in situ*. The substrate scope of this versatile process was ascertained *via* the synthesis of 11 diverse derivatives under green and mild conditions. The prepared phthalimides are attractive starting points for potential drug discovery, and further investigations to assess their pharmaceutical activities are ongoing in our research group.

EXPERIMENTAL SECTION

General Information. All reactions were performed by the QSONICA Q700 sonicator at an amplitude of 60% and a frequency of 20 kHz. The temperature of the reaction under US irradiation was monitored using a mercury laboratory thermometer. All reactions were monitored by thin-layer chromatography (TLC) on Merck silica gel 60 F254 plates. Column chromatography purification was carried out on silica gel (63−200 mesh ASTM). Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were recorded as KBr pellets on a Nicolet FTIR 100 spectrophotometer. ^{1}H NMR (500, 300 MHz) and ^{13}C NMR (125, 75 MHz) spectra were obtained using Bruker DRX-500 Avance and Bruker DRX-300 Avance spectrometers. All NMR spectra were recorded at rt in dimethyl sulfoxide (DMSO)-d_6 and $CDCl_3$. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane reference. Coupling constants (J values) are reported in hertz (Hz), and standard abbreviations were used to indicate spin multiplicities. Elemental analyses for C, H, and N were performed using a Heraeus CHN−O-Rapid analyzer. Mass spectra were recorded on a Finnigan-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. All chemicals and solvents were purchased from Merck or Aldrich and were used without further purification. Starting materials were synthesized according to the procedures reported in the literature.[18,29] A single crystal of compounds **6a′** was formed in DMSO.

*General Procedure for Preparation of Compounds **6a**−**6h** and **6a′**−**6c′**.* To a mixture of amine (1.0 mmol) and carbon disulfide (115 mg, 1.5 mmol) in EtOH (5 mL), dimethyl acetylenedicarboxylate (DMAD) (142 mg, 1.0 mmol) was added. Then, the mixture was subjected to US irradiation (20 kHz) at ambient temperature. The amplitude of the US waves was fixed at 60%. The reaction was accomplished within 5 min, then α,α-dicyanoolefine (1.0 mmol) and Et_3N (101 mg, 1.0 mmol) were added. After 15−20 min continuous irradiation, the reaction was completed and a yellow solid was isolated by simple filtration [derivatives **6a**−**6h** were purified by column chromatography (hexane/AcOEt, 4/1, v/v) and derivatives **6a′**−**6c′** were purified by washing with EtOH twice.].

Spectral Data of the Compounds. *4-Amino-2-benzyl-1,3-dioxo-6-phenyl-5-isoindolinecarbonitrile (**6a**).* Yield: 0.276 g (78%); yellow powder, mp 211−215 °C. IR (KBr, cm^{-1}) ν_{max}: 3502 and 3395 (NH_2), 2212 (CN), 1759 and 1706 (NC═O), 1620 and 1582 (C═C of Ar) cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.54−7.56 (m, 3H), 7.50 (d, 2H, $^3J_{HH}$ = 7.0 Hz), 7.41 (d, 2H, $^3J_{HH}$ = 7.5 Hz), 7.33 (t, 2H, $^3J_{HH}$ = 7.4 Hz), 7.28 (t, 1H, $^3J_{HH}$ = 7.2 Hz), 7.22 (s, 1H), 6.00 (br s, 2H), 4.82 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 168.6, 166.8, 153.5, 147.4, 137.3, 136.0, 129.9, 128.9, 128.7, 128.5, 128.4, 127.9, 115.4, 113.1, 110.3, 100.9, 41.6. MS m/z: 353 (M^+), 324, 248, 220, 192, 91. Anal. Calcd for $C_{22}H_{15}N_3O_2$ (353.37): C, 74.78; H, 4.28; N, 11.89%. Found: C, 74.80; H, 4.27; N, 11.90%.

*4-Amino-2-benzyl-6-(4-bromophenyl)-1,3-dioxo-5-isoindoline-carbonitrile (**6b**).* Yield: 88% (0.380 g); yellow powder, mp 268−272

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°C. IR (KBr, cm^{-1}) ν_{max}: 3487 and 3384 (NH_2), 2214 (CN), 1756 and 1704 (NC═O), 1621, 1603 and 1585 (C═C of Ar). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.65 (d, 2H, $^3J_{HH}$ = 8.5 Hz), 7.42 (d, 2H, $^3J_{HH}$ = 8.5 Hz), 7.41 (d, 2H, $^3J_{HH}$ = 7.1 Hz), 7.34 (t, 2H, $^3J_{HH}$ = 7.5 Hz), 7.29 (t, 1H, $^3J_{HH}$ = 7.1 Hz), 7.18 (s, 1H), 6.00 (br s, 2H), 4.82 (2H, s). $^3C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 168.4, 166.7, 152.1, 147.4, 136.2, 136.1, 135.9, 132.2, 129.9, 128.7, 128.5, 128.0, 124.5, 115.1, 112.8, 110.7, 100.6, 41.7. MS: *m/z* 432 (M^+), 415, 192, 164, 91. Anal. Calcd for $C_{22}H_{14}BrN_3O_2$ (432.27): C, 61.13; H, 3.26; N, 9.72%. Found: C, 61.15; H, 3.27; N, 9.74%.

*4-Amino-2-benzyl-6-(4-chlorophenyl)-1,3-dioxo-5-isoindolinecarbonitrile (**6c**).* Yield: 86% (0.335 g); yellow powder, mp 249−252 °C. IR (KBr, cm^{-1}) ν_{max}: 3489 and 3385 (NH_2), 2215 (CN), 1756 and 1703 (NC═O), 1622, 1600 and 1585 (C═C of Ar). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.49 (s, 4H), 7.41 (d, 2H, $^3J_{HH}$ = 7.6 Hz), 7.33 (t, 2H, $^3J_{HH}$ = 7.1 Hz), 7.29 (t, 1H, $^3J_{HH}$ = 7.4 Hz), 7.18 (s, 1H), 6.01 (br s, 2H), 4.82 (s, 2H). $^3C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 168.4, 166.7, 152.1, 147.4, 136.3, 136.2, 135.9, 135.6, 129.7, 129.2, 128.7, 128.5, 127.9, 115.2, 112.9, 110.6, 100.7, 41.7. MS *m/z*: 388 (M^+), 369, 192, 91. Anal. Calcd for $C_{22}H_{14}ClN_3O_2$ (387.82): C, 68.13; H, 3.64; N, 10.84%. Found: C, 68.15; H, 3.63; N, 10.83%.

*4-Amino-2-benzyl-6-(4-methoxyphenyl)-1,3-dioxo-5-isoindolinecarbonitrile (**6d**).* Yield: 76% (0.291 g); yellow powder, mp 231−234 °C. IR (KBr, cm^{-1}) ν_{max}: 3483 and 3376 (NH_2), 2212 (CN), 1755 and 1703 (NC═O), 1621 and 1602 (C═C of Ar), 1259 (C−O). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.53 (d, 2H, $^3J_{HH}$ = 8.7 Hz), 7.42 (d, 2H, $^3J_{HH}$ = 7.5 Hz), 7.34 (t, 2H, $^3J_{HH}$ = 7.2 Hz), 7.31 (t, 1H, $^3J_{HH}$ = 7.2 Hz), 7.21 (s, 1H), 7.03 (d, 2H, $^3J_{HH}$ = 8.8 Hz), 5.98 (br s, 2H), 4.82 (s, 2H), 3.88 (s, 3H). $^3C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 168.6, 166.9, 161.0, 153.2, 147.5, 136.1, 136.0, 129.9, 129.6, 128.7, 128.5, 127.9, 115.7, 114.4, 112.9, 109.7, 100.4, 55.4, 41.6. MS: *m/z* 383 (M^+), 365, 278, 250, 91. Anal. Calcd for $C_{23}H_{17}N_3O_3$ (383.40): C, 72.05; H, 4.47; N, 10.96%. Found: C, 72.07; H, 4.45; N, 10.95%.

*4-Amino-2-benzyl-6-(4-methylphenyl)-1,3-dioxo-5-isoindolinecarbonitrile (**6e**).* Yield: 73% (0.270 g); yellow powder, mp 236−239 °C. IR (KBr, cm^{-1}) ν_{max}: 3494 and 3390 (NH_2), 2213 (CN), 1756 and 1704 (NC═O), 1620 and 1583 (C═C of Ar). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.47 (d, 2H, $^3J_{HH}$ = 8.2 Hz), 7.42 (d, 2H, $^3J_{HH}$ = 8.2 Hz), 7.29−7.37 (m, 5H), 7.22 (s, 1H), 5.98 (br s, 2H), 4.83 (s, 2H), 2.44 (s, 3H). $^3C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 168.6, 166.9, 153.6, 147.4, 140.2, 136.0, 136.0, 134.4, 129.6, 128.7, 128.5, 128.3, 127.9, 115.5, 113.0, 110.1, 100.1, 41.6, 21.3. MS: *m/z* 367 (M^+), 349, 234, 205, 91. Anal. Calcd for $C_{23}H_{17}N_3O_2$ (367.40): C, 75.19; H, 4.66; N, 11.44%. Found: C, 75.20; H, 4.64; N, 11.45%.

*4-Amino-6-(4-chlorophenyl)-2-(4-methylbenzyl)-1,3-dioxo-5-isoindolinecarbonitrile (**6f**).* Yield: 67% (0.271 g); yellow powder, mp 234−237 °C. IR (KBr, cm^{-1}) ν_{max}: 3491, 3467, 3387, and 3364 (NH_2), 2215 (CN), 1759 and 1703 (NC═O), 1624 and 1587 (C═C of Ar), 1093 (C−O). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.49 (s, 4H), 7.30 (d, 2H, $^3J_{HH}$ = 7.9 Hz), 7.17 (s, 1H), 7.13 (d, 2H, $^3J_{HH}$ = 7.9 Hz), 6.00 (br s, 2H), 4.78 (s, 2H), 2.32 (s, 3H). $^3C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 168.5, 166.7, 152.0, 147.3, 137.8, 136.3, 136.2, 135.6, 132.9, 129.7, 129.4, 129.2, 128.5, 115.2, 112.8, 110.7, 100.6, 41.4, 21.1; MS *m/z*: 401 (M^+), 386, 310, 192, 105. Anal. Calcd for $C_{23}H_{16}ClN_3O_2$ (401.84): C, 68.74; H, 4.01; N, 10.46%. Found: C, 68.79; H, 4.02; N, 10.47%.

*4-Amino-6-(4-methoxyphenyl)-2-(4-methylbenzyl)-1,3-dioxo-5-isoindolinecarbonitrile (**6g**).* Yield: 75% (0.300 g); yellow powder, mp 247−249 °C. IR (KBr, cm^{-1}) ν_{max}: 3500 and 3393 (NH_2), 2213 (CN), 1757 and 1699 (NC═O), 1621 and 1583 (C═C of Ar), 1199 (C−O). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.54 (d, 2H, $^3J_{HH}$ = 8.8 Hz), 7.32 (d, 2H, $^3J_{HH}$ = 7.9 Hz), 7.20 (s, 1H), 7.15 (d, 2H, $^3J_{HH}$ = 7.7 Hz), 7.03 (d, 2H, $^3J_{HH}$ = 8.8 Hz), 5.98 (br s, 2H), 4.79 (s, 2H), 3.89 (s, 3H), 2.33 (s, 3H). $^3C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 168.6, 167.0, 161.0, 153.2, 147.4, 137.7, 136.0, 133.1, 129.9, 129.6, 129.4, 128.5, 115.7, 114.4, 112.9, 109.7, 100.3, 55.4, 41.3, 21.1. MS *m/z*: 397 (M^+), 382, 368, 305, 251, 105. Anal. Calcd for $C_{24}H_{19}N_3O_3$ (397.43): C, 72.53; H, 4.82; N, 10.57%. Found: C, 72.51; H, 4.84; N, 10.58%.

*2-Allyl-4-amino-1,3-dioxo-6-phenyl-5-isoindolinecarbonitrile (**6h**).* Yield: 80% (0.242 g); yellow powder, mp 185−188 °C. IR (KBr, cm^{-1}) ν_{max}: 3455 and 3353 (NH_2), 2218 (CN), 1752 and 1702 (NC═O), 1626 and 1601 (C═C of Ar). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.52−7.59 (m, 5H), 7.25 (s, 1H), 6.03 (br s, 2H), 5.89 (ddt, 1H, $^3J_{HH}$ = 16.2 Hz, $^3J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 5.6 Hz), 5.28 (d, 1H, $^3J_{HH}$ = 16.2 Hz), 5.23 (d, 1H, $^3J_{HH}$ = 10.9 Hz), 4.28 (1H, d, $^3J_{HH}$ = 5.6 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 168.5, 166.7, 153.5, 147.4, 137.3, 136.0, 131.2, 129.9, 128.9, 128.4, 118.0, 115.4, 113.0, 110.3, 100.9, 40.1. MS *m/z*: 303 (M^+), 285, 192, 166, 71, 57. Anal. Calcd for $C_{18}H_{13}N_3O_2$ (303.31): C, 71.28; H, 4.32; N, 13.85%. Found: C, 71.33; H, 4.45; N, 13.99%.

*4-Amino-2-benzyl-1,3,10-trioxo-1,2,3,10-tetrahydroindeno[2,1-e]isoindole-5-carbonitrile (**6a′**).* Yield: 75% (0.284 g); yellow powder, mp 338−341 °C. IR (KBr, cm^{-1}) ν_{max}: 3423 and 3309 (NH_2), 2221 (CN), 1764 and 1703 (C═O and NC═O), 1626, 1621, and 1580 (C═C of Ar). ^1H NMR (DMSO-d_6, 300 MHz): δ 8.12 (d, 1H, $^3J_{HH}$ = 7.4 Hz), 7.76 (s br, 2H), 7.67 (t, 1H, $^3J_{HH}$ = 7.6 Hz), 7.61 (d, 1H, $^3J_{HH}$ = 7.1 Hz), 7.54 (t, 1H, $^3J_{HH}$ = 7.4 Hz), 7.24−7.33 (5H, m), 4.69 (s, 2H). $^3C\{^1H\}$ NMR (DMSO-d_6, 75 MHz): δ 185.4, 168.1, 168.0, 150.8, 139.3, 136.3, 135.1, 135.0, 133.9, 128.4, 127.5, 127.4, 127.4, 123.9, 122.3, 114.4, 110.2, 100.7, 40.8. MS *m/z*: 379 (M^+), 361, 335, 247, 220, 191, 164, 91. Anal. Calcd for $C_{23}H_{13}N_3O_3$ (379.37): C, 72.82; H, 3.45; N, 11.08%. Found: C, 72.81; H, 3.46; N, 11.05%; crystal data for **6a′** $C_{23}H_{13}N_3O_3$ (CCDC 1955507): M_W = 379.36, monoclinic, $P21/c$, a = 12.122(2) Å, b = 16.216(3) Å, c = 8.839(2) Å, α = 90.00(3), β = 91.52(3), γ = 90.00(3), V = 1737.0(6) $Å^3$, Z = 1, Dc = 1.451 mg/m^3, $F(000)$ = 784, crystal dimension 0.30 × 0.30 × 0.30 mm, radiation, Mo Kα (λ = 0.71073 Å), 1.680 ≤ 2θ ≤ 27.589, intensity data were collected at 136(2) K with a Bruker APEX area-detector diffractometer and employing a $\omega/2\theta$ scanning technique in the range of $-15 \le h \le 15$, $-21 \le k \le 21$, $-11 \le l \le 11$; the structure was solved by a direct method, all non-hydrogen atoms were positioned and anisotropic thermal parameters refined from 4019 observed reflections with R (into) = 0.0232 by a full-matrix least-squares technique converged to $R1$ = 0.0355 and w$R2$ = 0.0920 [$I > 2\text{sigma}(I)$].

*2-Allyl-4-amino-1,3,10-trioxo-1,2,3,10-tetrahydroindeno[2,1-e]-isoindole-5-carbonitrile (**6b′**).* Yield: 77% (0.253 g); yellow powder, mp 317−319 °C. IR (KBr, cm^{-1}) ν_{max}: 3466 and 3317 (NH_2), 2216 (CN), 1762, 1717, and 1705 (C═O and NC═O), 1621, 1607, and 1579 (C═C of Ar). ^1H NMR (DMSO-d_6, 300 MHz): δ 8.11 (d, 1H, $^3J_{HH}$ = 7.7 Hz), 7.72 (t, 1H, $^3J_{HH}$ = 6.9 Hz), 7.63 (d, 1H, $^3J_{HH}$ = 6.7 Hz), 7.60 (t, 1H, $^3J_{HH}$ = 7.6 Hz), 7.55 (br s, 1H), 5.85 (ddt, 1H, $^3J_{HH}$ = 17.1 Hz, $^3J_{HH}$ = 8.3 Hz, $^3J_{HH}$ = 5.4 Hz), 5.17 (d, 1H, $^3J_{HH}$ = 17.1 Hz), 5.14 (d, 1H, $^3J_{HH}$ = 8.3 Hz), 4.11 (s, 2H). $^3C\{^1H\}$ NMR (DMSO-d_6, 75 MHz): δ 189.1, 167.9, 167.8, 152.5, 150.7, 139.2, 135.0, 132.4, 132.1, 132.0, 124.0, 123.8, 122.3, 116.6, 114.4, 107.7, 100.0, 40.3. MS *m/z*: 329 (M^+), 311, 246, 218, 189, 163. Anal. Calcd for $C_{19}H_{11}N_3O_3$ (329.31): C, 69.30; H, 3.37; N, 12.76%. Found: C, 69.28; H, 3.35; N, 12.74%.

*4-Amino-2-butyl-1,3,10-trioxo-1,2,3,10-tetrahydroindeno[2,1-e]-isoindole-5-carbonitrile (**6c′**).* Yield: 73% (0.252 g); yellow powder, mp 320−323 °C; IR (KBr, cm^{-1}) ν_{max}: 3466 and 3316 (NH_2), 2216 (CN), 1762, 1717 and 1705 (NC═O and C═O), 1621 and 1606 (C═C of Ar). ^1H NMR (DMSO-d_6, 300 MHz): δ 8.15 (d, 1H, $^3J_{HH}$ = 7.6 Hz), 7.73 (s br, 2H), 7.73 (td, 1H, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 0.8 Hz), 7.65 (dd, 1H, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 0.8 Hz), 7.58 (td, 1H, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 0.8 Hz), 3.49 (t, 2H, $^3J_{HH}$ = 7.1 Hz), 1.55 (pen, 2H, $^3J_{HH}$ = 7.1 Hz), 1.28 (sex, 2H, $^3J_{HH}$ = 7.4 Hz), 0.84 (t, 3H, $^3J_{HH}$ = 7.4 Hz). $^3C\{^1H\}$ NMR (DMSO-d_6, 75 MHz): δ 185.4, 168.3, 168.8, 153.8, 150.6, 139.2, 135.0, 135.0, 133.9, 132.3, 123.9, 122.2, 117.8, 114.3, 110.3, 92.9, 37.0, 29.8, 19.4, 13.4. MS *m/z*: 345 (M^+), 303, 246, 218, 164. Anal. Calcd for $C_{20}H_{15}N_3O_3$ (345.35): C, 69.56; H, 4.38; N, 12.17%. Found: C, 69.56; H, 4.39; N, 12.15%.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02245.

Copies of IR and mass spectra, ^1H and ^{13}C NMR spectra of products, and ORTEP/X-ray structure for **6a′** (PDF)

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CCDC 1955507 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

Abdolali Alizadeh − *Department of Chemistry, Tarbiat Modares University, 14115-175 Tehran, Iran;* orcid.org/0000-0002-1842-7219; Phone: +98-21-82884402; Email: aalizadeh@rmodares.ac.ir; Fax: +98-21-82883455

Authors

Behnaz Farajpour − *Department of Chemistry, Tarbiat Modares University, 14115-175 Tehran, Iran*

Tim-Oliver Knedel − *Institut für Anorganische Chemie, und Strukturchemie Heinrich-Heine-Universität Düsseldorf, I40225 Düsseldorf, Germany*

Christoph Janiak − *Institut für Anorganische Chemie, und Strukturchemie Heinrich-Heine-Universität Düsseldorf, I40225 Düsseldorf, Germany;* orcid.org/0000-0002-6288-9605

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02245

Notes

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DEDICATION

Dedicated to Professor Dr. Issa Yavari on the occasion of his 71st birthday.

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