Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 49 (2008) 149–152

Studies on isocyanides: synthesis of tetrazolyl-isoindolinones via tandem Ugi four-component condensation/intramolecular amidation

Carlos F. Marcos,[a] Stefano Marcaccini,[b,*] Gloria Menchi,[b] Roberto Pepino[b] and Tomás Torroba[c]

[a]*Departamento de Química Orgánica, Facultad de Veterinaria, Universidad de Extremadura, Avenida de la Universidad s/n, E-10071 Cáceres, Spain*
[b]*HeteroBioLab, Dipartimento di Chimica Organica, Università di Firenze, Via della Lastruccia 13, I-50019 Sesto Fiorentino (FI), Italy*
[c]*Departamento de Química, Facultad de Ciencias, Universidad de Burgos, Plaza Misael Bañuelos s/n, E-09001 Burgos, Spain*

Received 8 October 2007; accepted 29 October 2007
Available online 4 November 2007

Dedicated to the memory of our valued co-worker and friend Cecilia Polo Polo

Abstract—The Ugi four-component condensation between methyl *o*-formylbenzoates **1**, anilines **2a**–**c**, isocyanides **3**, and trimethylsilyl azide (**4**) afforded the expected Ugi adducts **5a**–**d**, which were cyclized to the title compounds **6a**–**d** upon treatment with sodium ethoxide in ethanol. Starting from aralkyl- or alkylamines **2d**–**g** the Ugi adducts underwent a spontaneous cyclization to tetrazolyl-isoindolinones **6e**–**j**.

The tetrazole nucleus is found in many biologically active products.[1] The activity of certain derivatives of this heterocyclic system on the CNS was recognized many years ago.[2] Among the pharmaceutically important tetrazoles the widely used angiotensin II antagonist Losartan, marketed by Merck, deserves a special mention. Tetrazole derivatives also display interesting non-biological properties. For example, their usefulness as primary explosives[3] and ligands[4] has recently been reported. A considerable attention has been focused on 1,5-disubstituted tetrazoles in the field of peptide chemistry because they are *cis*-amide bond mimics.[5] For example, analogous of somatostatine,[6] bradykinin,[7] and deaminooxytocin[8] containing the above core has been described.

A great deal of work has been devoted to the study of 2,3-dihydro-1*H*-isoindol-1-ones (isoindolinones) since this moiety is found in a wide variety of natural and synthetic products,[9] which display very interesting activities. Among them the alkaloids lennoxamine, aristoyagonine, nuevamine, and chilenine are specially noteworthy[10] and a number of researchers have been involved in their synthesis.[11] Interesting natural products structurally related to the indolinone alkaloids have been isolated and synthesized.[12] Other 3-substituted and 2,3-disubstituted isoindolinones are pharmaceutically relevant because of their capabilities to act as HIV-1 reverse transcriptase inhibitors,[13] anxiolytics,[14] and dopamine D_4[15] and 5-HT[16] receptor antagonists.

Interestingly, both systems are easily obtainable by means of isocyanide-based multicomponent reactions. The formation of isoindolin-1-ones via intramolecular Ugi-4CC is well documented.[17] The synthesis of 1,5-disubstituted tetrazoles is one of the earlier achievements of the Ugi-4CC: in this case hydrazoic acid plays the role of the acid component.[18] The use of trimethylsilyl azide as hydrazoic acid source has further increased the versatility of this route.[19]

In recent years, a variety of very interesting substituted[20] and fused tetrazoles[19,21] have been prepared via Ugi-4CC by employing starting products containing suitable additional functional groups.

Keeping in mind the above results and our interest in the synthesis of heterocyclic systems by means of post-condensation modifications of the Ugi reaction[22] we

* Corresponding author. Tel.: +39 055 457 3510; fax: +39 055 457 3531; e-mail: stefano@marcaccini.unifi.it

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.10.154

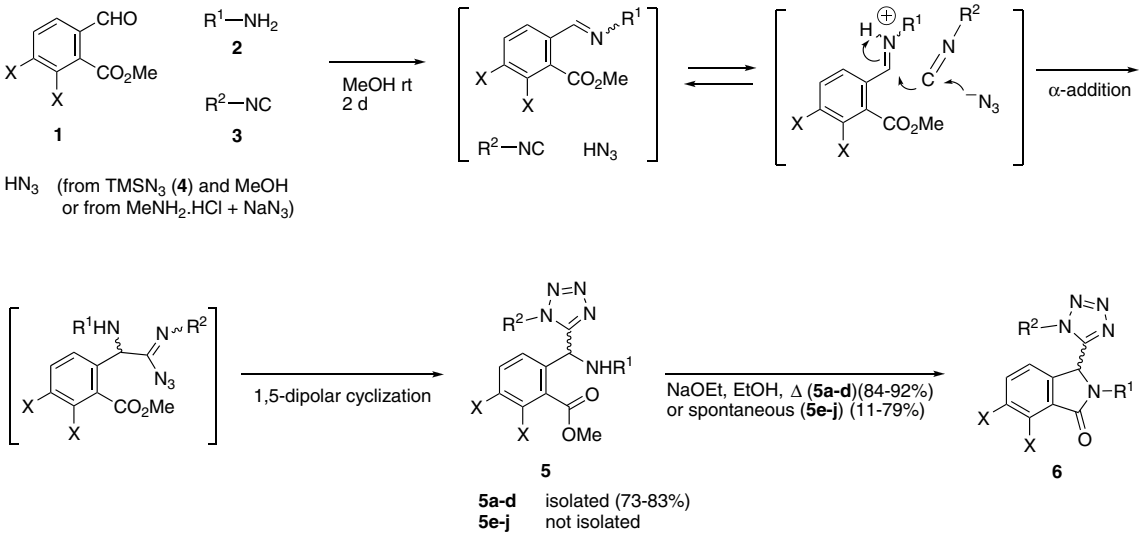
decided to attempt the synthesis of a series of isoindolin-1-ones bearing a 1-substituted tetrazol-5-yl moiety in position 3.

The synthesis was accomplished by reacting methyl *o*-formylbenzoates **1** as bireactive carbonyl components,[23] amines **2**, isocyanides **3**, and trimethylsilyl azide (**4**).

All of the starting products are commercially available or easily obtainable. Methyl *o*-formylbenzoates **1** were easily prepared starting from the commercially available 2-formylbenzoic and opianic acids.[24] 4-Ethoxyphenyl isocyanide (**3c**) was prepared from *p*-phenetidine.[25]

The Ugi reactions took place smoothly, by simple stirring the reactants in methanol for 2 days at room temperature. The preparation of compound **6h** was achieved following the traditional Ugi procedure—in which the amine and hydrazoic acid were generated in situ by reacting the amine hydrochloride with sodium azide—with equally good results (Scheme 1).

When anilines **2a–c** were employed as the starting amines the Ugi adducts **5a–d** were isolated in good yields.[26] The Ugi adducts **5e–j** arising from aralkyl- or alkylamines **2d–g** were never detected because of the enhanced nucleophilic character of the amino group, which is strong enough to allow the attack onto the ester group with subsequent cyclization to isoindolinones **6e–j**.[27] However, the Ugi adducts **5a–d** were easily cyclized to the corresponding isoindolinones **6a–d** in very good yields upon treatment with sodium ethoxide in ethanol.[28]



1	X
a	H
b	OCH_3

2	R^1
a	4-$CH_3C_6H_4$
b	4-ClC_6H_4
c	4-FC_6H_4
d	$C_6H_5CH_2$
e	4-$ClC_6H_4CH_2$
f	C_5H_9O[a]
g	CH_3[b]

a) Tetrahydrofurfurylmethyl.
b) Starting amine as hydrochloride.

3	R^2
a	$C_6H_5CH_2$
b	*c*-C_6H_{11}
c	4-$C_2H_5OC_6H_4$
d	4-$CH_3C_6H_4SO_2CH_2$

5,6	X	R^1	R^2	Yield (%) **5**	Products **5** Mp °C[a]	Yield (%) **6**	Products **6** Mp °C[a]
a	H	4-$CH_3C_6H_4$	$C_6H_5CH_2$	78	132-135	90	186-187
b	H	4-$CH_3C_6H_4$	*c*-C_6H_{11}	83	178-179	92	171-173
c	H	4-ClC_6H_4	$C_6H_5CH_2$	73	151-152	88	193-195
d	H	4-FC_6H_4	*c*-C_6H_{11}	75	150-151	84	120-121[b]
e	H	4-$ClC_6H_4CH_2$	*c*-C_6H_{11}			74	170-171
f	H	$C_6H_5CH_2$	4-$CH_3C_6H_4SO_2CH_2$			11[c]	204-205
g	H	C_5H_9O	4-$C_2H_5OC_6H_4$			77	144-145
h	H	CH_3	4-$C_2H_5OC_6H_4$			68	138-141
i	OCH_3	$C_6H_5CH_2$	*c*-C_6H_{11}			79	139-140
j	OCH_3	4-$ClC_6H_4CH_2$	*c*-C_6H_{11}			71	145-146

a) Solvent EtOH unless otherwise stated. b) Solvent MeOH/*i*-Pr_2O. c) Product isolated by filtration; after column chromatography **6f** was obtained in 52% yield.

Scheme 1. Synthesis of tetrazolyl-isoindolinones via Ugi-CC/intramolecular amidation.

The structure of the Ugi four-component adducts **5a–d** was in agreement with their IR and ^{1}H NMR spectra. In the IR spectra two strong absorptions at about 3350 and 1700 cm^{-1} were detected, due to the secondary amino group and to the ester carbonyl group, respectively. In the ^{1}H NMR spectra a singlet signal at about 3.80 δ, due to the ester methyl protons was detected. Furthermore, a doublet signal at about 4.60 δ due to the NH proton coupled with the benzyl proton at about 7.00 δ as seen. The benzyl proton doublet was not always clearly detected because of the overlapping with the aromatic protons. The comparison of the IR and ^{1}H NMR spectra of **5a–d** with those of **6a–d** clearly confirmed the cyclization. In the IR spectra of **6a–d** no NH peak was detected and the CO peak was shifted to about 1690 cm^{-1} in agreement with the presence of a γ-lactam ring. As expected in the ^{1}H NMR spectra of **6a–d** the signals attributable to the ester methyl protons and to the NH proton disappeared and a singlet signal at about 6.90 δ due to the benzyl proton was detected. In the ^{1}H NMR spectra of **6e–j** the benzyl proton singlet was always clearly detected at about 6.00 δ; consequently, it was well separated from the aromatic protons signals.

In conclusion, we have developed a method for assembling two interesting heterocyclic systems by means of a very simple experimental procedure. The desired products **6e–j** were obtained by mixing the reactants at room temperature and precipitated from the mother liquors in a pure form, avoiding the need of tedious work-up procedures. When anilines were employed as the starting amines the Ugi adducts were easily isolated and cyclized to **6a–d** in a very simple and rapid fashion.

References and notes

1. (a) Butler, R. N. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 4, pp 621–678; (b) Himo, F.; Demko, Z. P.; Noodleman, L. *J. Org. Chem.* **2003**, *68*, 9076–9080, and references cited therein; (c) Upadhayaya, R. S.; Sinha, N.; Jain, S.; Kishore, N.; Chandra, R.; Arora, S. K. *Bioorg. Med. Chem.* **2004**, *12*, 2225–2228.
2. Gross, E. G.; Featherstone, R. M. *J. Pharmacol. Exp. Ther.* **1946**, *87*, 299–305.
3. Huynh, M. H. V.; Coburn, M. D.; Meyer, T. J.; Wetzler, M. *Proc. Natl. Acad. Sci. U.S.A* **2006**, *103*, 10322–10327.
4. Gao, E.-Q.; Liu, N.; Cheng, A.-L.; Gao, S. *Chem. Commun.* **2007**, 2470–2472.
5. (a) Zabrocki, J.; Smith, G. D.; Dunbar, J. B., Jr.; Iijima, H.; Marshall, G. R. *J. Am. Chem. Soc.* **1988**, *110*, 5875–5880; (b) Kaczmarek, K.; Jankowski, S.; Siemion, I. Z.; Wieczorek, Z.; Benedetti, E.; Di Lello, P.; Isernia, C.; Saviano, M.; Zabrocki, J. *Biopolymers* **2002**, *63*, 343–357.
6. Beusen, D. D.; Zabrocki, J.; Slomczynska, U.; Head, R. D.; Kao, J.; Marshall, G. R. *Biopolymers* **1995**, *36*, 181–200.
7. Zabrocki, J.; Dunbar, J. B. Jr.; Marshall, K. W.; Toth, M. V.; Marshall, G. R. *J. Org. Chem.* **1992**, *57*, 202–209.
8. Lebl, M.; Slaninoca, J.; Johnson, R. L. *Int. J. Pept. Protein Res.* **1989**, *33*, 16–21.
9. Gai, X.; Grigg, R.; Tossapol, K.; Rajviroongit, S.; Sridharan, V.; Zhang, L.; Collard, S.; Keep, A. *Tetrahedron Lett.* **2003**, *44*, 7441–7443, and references cited therein.
10. Sarang, P. S.; Yadav, A. A.; Patil, P. S.; Krishna, U. M.; Trivedi, G. K.; Salunke, M. M. *Synthesis* **2007**, 1091–1095, and references cited therein.
11. (a) Ishibashi, H.; Kawanami, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 817–821; (b) Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. *Tetrahedron* **2000**, *56*, 1491–1499; (c) Comins, D. L.; Schilling, S.; Zhang, Y. *Org. Lett.* **2005**, *7*, 95–98.
12. (a) Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. *J. Org. Chem.* **1998**, *63*, 3128–3132; (b) Rys, V.; Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron* **2003**, *59*, 6615–6619.
13. (a) De Clercq, E. *J. Med. Chem.* **1995**, *38*, 2491–2517; (b) Mertens, A.; Zilch, H.; König, B.; Schäfer, W.; Poll, T.; Kampe, W.; Seidel, H.; Leser, U.; Leinert, H. *J. Med. Chem.* **1993**, *36*, 2526–2535.
14. (a) Suzuki, M.; Uchiumi, M.; Marasaki, M. *Psychopharmacology* **1995**, *121*, 442–450; (b) Takahashi, I.; Kawakami, T.; Hirano, E.; Yokota, H.; Kitajima, H. *Synlett* **1996**, 353–355.
15. Belliotti, T. R.; Brink, W. A.; Kesten, S. R.; Rubin, J. R.; Wustrow, D. J.; Zoski, K. T.; Whetzel, S. Z.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1499–1502.
16. Zhuang, Z. P.; Kung, M. P.; Mu, M.; Kung, H. F. *J. Med. Chem.* **1998**, *41*, 157–166.
17. (a) Hanusch-Kompa, G.; Ugi, I. *Tetrahedron Lett.* **1998**, *39*, 2725–2728; (b) Ley, S. V.; Taylor, S. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1813–1816; (c) Zhang, J.; Jacobson, A.; Rusche, J. R.; Herlihy, W. *J. Org. Chem.* **1999**, *64*, 1074–1076.
18. (a) Ugi, I.; Steinbruckner, C. *Chem. Ber.* **1961**, *94*, 734–742; (b) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 8–21.
19. Bienaymé, H.; Bouzid, K. *Tetrahedron Lett.* **1998**, *39*, 2735–2738.
20. Nixey, T.; Hulme, C. *Tetrahedron Lett.* **2002**, *43*, 6833–6835.
21. (a) Nixey, T.; Kelly, M.; Hulme, C. *Tetrahedron Lett.* **2000**, *41*, 8729–8733; (b) Nixey, T.; Kelly, M.; Semin, D.; Hulme, C. *Tetrahedron Lett.* **2002**, *43*, 3681–3684.
22. (a) Marcaccini, S.; Torroba, T. *Org. Prep. Proced. Int.* **1993**, *25*, 141–208; (b) Marcaccini, S.; Torroba, T. Post-condensation Modifications of the Passerini and Ugi Reactions. In *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005; pp 33–75; (c) Ignacio, J. M.; Macho, S.; Marcaccini, S.; Pepino, R.; Torroba, T. *Synlett* **2005**, 3051–3054; (d) Sañudo, M.; Marcaccini, S.; Basurto, S.; Torroba, T. *J. Org. Chem.* **2006**, *71*, 4578–4584; (e) Neo, A. G.; Carrillo, R. M.; Barriga, S.; Momán, E.; Marcaccini, S.; Marcos, C. F. *Synlett* **2007**, 327–329.
23. While the manuscript was in preparation a paper dealing with the use of 2-formylbenzoic esters as bireactive materials for the synthesis of quinoline-based tetracycles via isocyanide multicomponent reaction appeared: Che, C.; Xiang, J.; Wang, G.-X.; Fathi, R.; Quan, J.-M.; Yang, Z. *J. Comb. Chem.*, Web release date: 18 August 2007, doi:10.1021/cc070058a.
24. Methyl 2-formylbenzoate **1a** was prepared from phthalaldehydic acid and methyl iodide in acetonitrile Ye, B.-H.; Naruta, Y. *Tetrahedron* **2003**, *59*, 3593–3601, Methyl opianate **1b** was best prepared by treating a suspension of finely powdered opianic acid in $Et_2O/CHCl_3$ (1:1) with ethereal diazomethane at 0 °C.

25. Neo, A. G.; Marcos, C. F.; Marcaccini, S.; Pepino, R. *Tetrahedron Lett.* **2005**, *46*, 7977–7979.

26. *Methyl 2-[(1-Benzyl-1H-tetrazol)-5-yl-(4-methylphenyl)-amino]methylbenzoate* (**5a**): A solution of methyl 2-formylbenzoate (**1a**) (328 mg, 2.0 mmol) in methanol (4.5 ml) was treated as quickly as possible with 4-toluidine (**2a**) (214 mg, 2.0 mmol), benzyl isocyanide (**3a**) (234 mg, 2.0 mmol), and trimethylsilyl azide (**4**) (230 mg, 2.0 mmol) in the order given. The resulting mixture was stirred at rt for 2 days and then cooled with ice-salt and filtered to give **5a** (612 mg, 74%) as white crystals. Mp 132–135 °C from EtOH. IR (KBr): 3356, 1706, 1620, 1527, 1273, 1261, 1071, 739, 717, 697 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 8.08 (d, $J = 7.7$ Hz, 1H, Ar-H), 7.60–7.33 (m, 2H, Ar-H), 7.28–7.16 (m, 5H, Ar-H), 6.93–6.87 (m, 3H, Ar-H+C*H*-NH), 6.35 (d, $J = 8.4$ Hz, 2H, Ar-H), 5.69 (AB system, 2H, CH_2Ar), 4.33 (d, $J = 8.8$ Hz, 2H, NH), 3.79 (s, 3H, OCH_3), 2.20 (s, 3H, CH_3Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 167.4 (s), 155.6 (s), 142.9 (s), 139.2 (s), 138.6 (s), 133.3 (s), 133.1 (d), 131.8 (s), 131.3 (d), 129.7 (d), 128.8 (d, 2C), 128.6 (d), 128.4 (d, 2C), 128.3 (d), 128.1 (d, 2C), 114.0 (d, 2C), 52.5 (d), 51.4 (t), 49.6 (q),20.6 (q). Anal. Calcd for $C_{24}H_{23}N_5O_2$: C, 69.72; H, 5.61; N, 16.94. Found: C, 69.89; H, 5.51; N, 17.03.
Ugi adducts **5b–d** were prepared in the same manner.

27. *2-(4-Chloro)benzyl-3-(1-cyclohexyl-1H-tetrazol)-5-yl-2,3-dihydro-1H-isoindol-1-one* (**6e**): A solution of methyl 2-formylbenzoate (**1a**) (328 mg, 2.0 mmol) in methanol (4.5 ml) was treated with 4-chlorobenzylamine (**2e**) (283 mg, 2.0 mmol), cyclohexyl isocyanide (**3b**) (218 mg, 2.0 mmol), and trimethylsilyl azide (**4**) (230 mg, 2.0 mmol) in the order given. The resulting mixture was stirred at rt for 2 days and then cooled with ice-salt and filtered to give **6e** (607 mg, 74%) as white crystals. Mp 170–171 °C from EtOH. IR (KBr): 2944, 2856, 1691, 1441, 1396, 1092, 1016, 848, 803, 722, 575 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 8.01 (m, 1H, Ar-H), 7.62–7.55 (m, 2H, Ar-H), 7.26–7.15 (m, 5H, Ar-H), 6.10 (s, 1H, CHN), 4.96 (d, $J = 14.6$ Hz, 1H, CH_2Ar), 4.09 (d, $J = 14.6$ Hz, 1H, CH_2Ar), 3.18–2.98 (m, 1H, H-1cyclohexyl), 1.90–0.45 (m, 10H cyclohexyl); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 167.5 (s), 149.3 (s), 140.2 (s), 134.1 (s), 133.2 (s), 132.9 (d), 131.3 (s), 130.1 (d, 2C), 129.3 (d), 129.0 (d, 2C), 124.5 (d), 123.0 (d), 58.9 (d), 54.4 (d), 44.7 (t), 32.7 (t), 32.3 (t), 25.3 (t), 25.2 (t), 24.5 (t). Anal. Calcd for $C_{22}H_{22}ClN_5O$: C, 64.78; H, 5.44; N, 17.17. Found: C, 64.55; H, 5.52; N, 16.98.
Compounds **6f,g,i,j** were prepared analogously.
3-[1-(4-Ethoxy)phenyl-1H-tetrazol]-5-yl-2,3-dihydro-2-methyl-1H-isoindol-1-one (**6h**): A stirred solution of methyl 2-formylbenzoate (**1a**) and methylamine hydrochloride (dried overnight over P_2O_5) (**2g**) (135 mg, 2.0 mmol) in MeOH (4 ml) was treated with 4-ethoxyphenyl isocyanide (**3d**) (294 mg, 2.0 mmol) and a saturated aqueous solution of sodium azide (130 mg, 0.2 mmol). The resulting mixture was stirred at rt for 2 days and then cooled with ice-salt and filtered. The collected solid was washed with cold *i*-Pr_2O (2 ml) and then with pentane. After air-drying the solid was stirred with water and filtered again to give **6h** (438 mg, 65%). Mp 138–141 °C from EtOH. IR (KBr): 1698, 1516, 1479, 1388, 1256, 1179, 1046, 735, 547 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.66–7.42 (m, 3H, Ar-H), 7.28–7.24 (m, 1H, Ar-H), 6.66–6.53 (m, 4H, Ar-H), 6.10 (s, 1H, CHN), 3.95 (q, $J = 7.0$ Hz, 2H, CH_2O), 2.92 (s, 3H, NCH_3), 1,37 (t, $J = 7.0$ Hz, 3H, CH_2–C*H*$_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 167.1 (s), 160.3 (s), 151.5 (s), 140.1 (s), 132.2 (d), 131.8 (s), 129.6 (d), 126.3 (d, 2C), 124.6 (s), 123.8 (d), 122.7 (d), 114.8 (d, 2C), 64.0 (t), 56.5 (d), 28.0 (q), 14.7 (q).
Anal. Calcd for $C_{18}H_{17}N_5O_2$: C, 64.47; H, 5.11; N, 20.88. Found: C, 64.29; H, 5.21; N, 21.05.

28. *3-(1-Benzyl-1H-tetrazol)-5-yl-2,3-dihydro-2-(4-methyl)-phenyl-1H-isoindol-1-one* (**6a**): A saturated solution of **5a** (207 mg, 0.5 mmol) in boiling ethanol was prepared in a large-mouthed small flask. The vessel was removed from the heating bath and the solution treated, as quickly as possible, with ethanolic EtONa (1 M, 0.5 ml, 0.5 mmol). The reaction mixture was allowed to stand for 5 min and then cooled at 0 °C. Cold EtOH (2 ml) was added and the resulting sludge was filtered with the aid of a spoon-shaped spatula to afford **6a** (172 mg, 90%) as a white solid. Mp 186–187 °C from EtOH. IR (KBr): 1695, 1519, 1456, 1367, 802, 722, 690, 509; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.86–7.81 (m, 1H, Ar-H), 7.50–7.45 (m, 2H, Ar-H), 7.37 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.20–7.00 (m, 6H, Ar-H), 6.85 (s, 1H, CHN), 6.58 (d, $J = 7.3$ Hz, 2H, Ar-H), 5.05 (AB system, 2H, CH_2Ar), 2.29, (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 166.4 (s), 150.9 (s), 138.6 (s), 135.5 (s), 133.6 (s), 133.1 (s), 131,9 (d), 131.7 (s), 130.0 (d, 2C), 129.9 (d, 2C), 128.7 (d, 2C), 128.4 (d), 126.7 (d), 124.6 (d), 122.9 (d), 120.0 (d, 2C), 55.6 (d), 51.5 (t), 21.0 (q). Anal. Calcd for $C_{23}H_{19}N_5O$: C, 72.42; H, 5.02; N, 18.36. Found: C, 72.46; H, 4.90; N, 18.59.
Compounds **6b–d** were prepared in a similar manner.