Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 323–326

Synthesis of substituted tetralones as intermediates of CNS agents via palladium-catalyzed cross-coupling reactions☆

María Torrado, Christian F. Masaguer and Enrique Raviña*

Departamento de Química Orgánica, Laboratorio de Química Farmacéutica, Facultad de Farmacia, Universidad de Santiago de Compostela, E-15782 Santiago de Compostela, Spain

Received 19 September 2006; revised 25 October 2006; accepted 27 October 2006
Available online 27 November 2006

Abstract—A series of substituted tetralones as intermediates of CNS agents has been synthesized via Pd-catalyzed coupling reactions of 3-(methoxycarbonyl)-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl trifluoromethanesulfonate (**5**) with a variety of organometallic reagents.

The discovery and development of novel therapeutics for schizophrenia, one of the most devastating brain disorders (affecting about 1% of the world's population), is now one of the most challenging areas of CNS research. The introduction of the butyrophenone haloperidol (Haldol®, Fig. 1) into the clinic in 1959 was a significant advancement in the treatment of schizophrenia, due to its efficacy in countering the hallucinatory and delusional (positive) symptoms of the disease.[1] However, haloperidol is ineffective in the treatment of negative symptoms and neurocognitive deficits,[2] a therapeutic profile that could be rationalized by the relatively low affinity for 5-HT_{2A} receptors compared to D_2 receptors.[3] On the other hand, the safety advantages of second-generation (atypical) antipsychotic drugs, characterized by their high affinity for serotonin 5-HT_{2A} receptors, have been questioned because of their propensity to induce weight gain and alter glucose and lipid metabolism.[4]

In the last few years we have been working on modulation of the butyrophenone system with the aim of combining antagonism at 5-HT_2 family and D_2 receptors in a single molecule.[5] We have reported the synthesis, pharmacological activity and molecular modelling of the aminoalkylbenzocycloalkanones **I** (Fig. 1), which

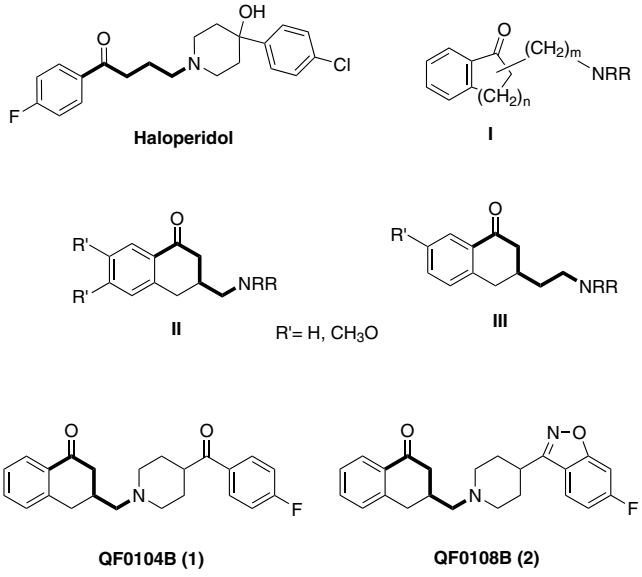


Figure 1.

are conformationally restricted butyrophenone analogues of haloperidol.[6] Among these compounds, the favourable pharmacological profile of the tetralone derivatives **II**[7] and **II**[8] has prompted us to explore the structure–activity relationships of this system as a scaffold for the design of new analogues of haloperidol. Aminobutyrophenones QF0104B (**1**) and QF0108B (**2**) (Fig. 1) showed high affinity for the 5-HT_{2A} receptor subtype with K_i values of 1.6 and 2.7 nM, respectively, with compound **1** being the most selective for the

Keywords: Palladium-catalyzed coupling reactions; Stille; Suzuki; Sonogashira; Cyanation.

☆ This is the 35th paper in the series 'Synthesis and CNS Activity of Conformationally Restricted Butyrophenones'.

* Corresponding author. Tel.: +34 981 563 100; fax: +34 981 594 912; e-mail: qofara@usc.es

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.10.154

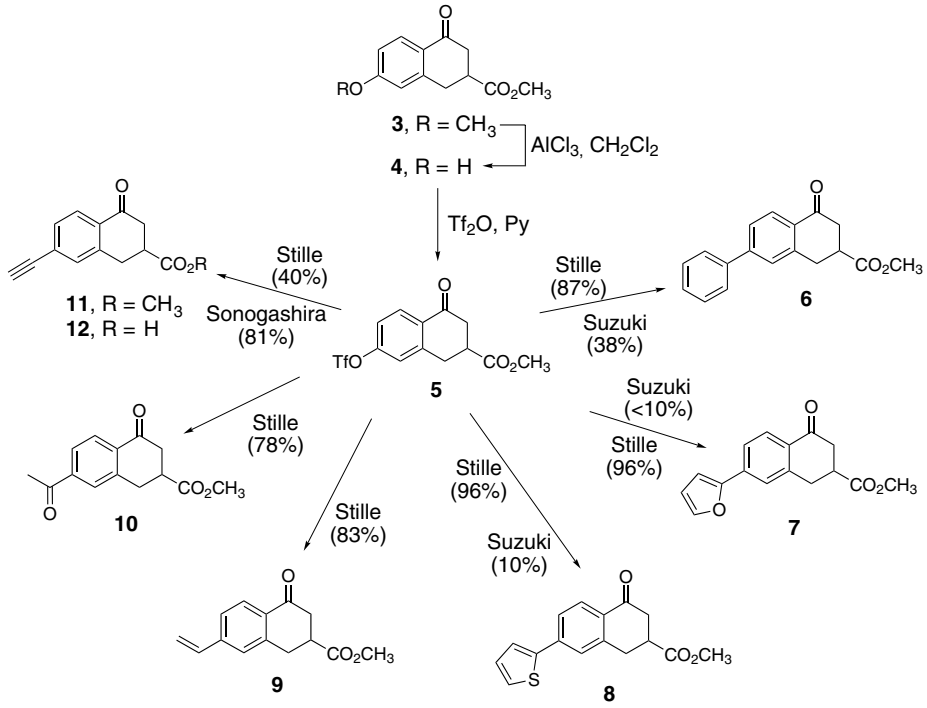
serotonin 5-HT_{2A} receptor subtype, with a 5-HT_{2A}/5-HT_{2C} K_i ratio as high as 150.[7] These compounds are also potent D_2 receptor antagonists, although they display K_i values higher than those at 5-HT_{2A} receptors.

In these series, our preliminary results showed that methoxy groups at the tetralone ring do not significantly affect the binding affinity towards any of the receptors studied, which suggests that their interaction with such receptors is not significant. However, a more in-depth study of the effect of substituents at the aromatic ring on affinity for serotonin and dopamine receptors is necessary. The addition of substituents to a lead structure is often used to find additional binding interactions with the target. This strategy involves the addition of hydrophobic regions by adding alkyl or aryl groups, and also other functional groups can be added to probe for extra hydrogen or ionic bonding interactions. In this letter, we report the synthesis of a series of substituted aminomethyltetralones through palladium-catalyzed coupling reactions, as intermediates in the synthesis of new CNS agents.

For this study, 3-(methoxycarbonyl)-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl trifluoromethanesulfonate (**5**) was used as the starting material, which was prepared by cleavage of the methylether group of the known compound **3**[7] (Scheme 1) with $AlCl_3$ in CH_2Cl_2, and subsequent reaction of the phenol derivative obtained (**4**) with trifluoromethanesulfonic anhydride in pyridine (66% yield, two steps).[9] The first reaction studied was the Suzuki arylation[10] of triflate **5** with boronic acids. Reactions were carried out by refluxing a mixture of **5** and the appropriate boronic acid (phenyl, 2-furyl or 2-thienyl) in the presence of a base, using tetrakis(triphenylphosphine)palladium(0) as a catalyst. After some optimization of the experimental conditions, for phenylboronic acid it was found that phenyl coupling of **5** involved heating in DMF in the presence of 1% $Pd(PPh_3)_4$ with 3 equiv of K_2CO_3. Under these conditions, the phenyltetralone (**6**) was obtained in 38% yield.

Disappointingly, all attempts to couple triflate **5** with 2-furylboronic or 2-thienylboronic acids under a variety of conditions were unsuccessful. Repeated assays where catalyst, base and solvent were varied afforded poor yields (<10%) of 7-furyltetralone **7**, or 7-thienyltetralone **8**,[11] leading in some cases to the formation of the detriflated compound (methyl 4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate) or the phenol derivative **4**.

Since Suzuki couplings of triflate **5** with phenyl- and heterocyclic boronic acids were unsatisfactory, we decided to apply the Stille methodology[12] for the cross-coupling arylation of **5**. In our hands, the reaction of the triflate derivative (**5**) with 1 equiv of tributyl- (or trimethyl-) phenylstannane and 10% $Pd(PPh_3)_4$ in the presence of LiCl (3 equiv) in dioxane at 110 °C under argon were the best conditions. Under these conditions, the 7-phenyltetralone derivative (**6**) was obtained in 86% yield (Table 1, entries 1 and 2).[13] Similarly, Stille coupling of **5** with 2-(tributylstannyl)furan (entry 3) or 2-(tributylstannyl)thiophene (entry 4) using the above-mentioned conditions led to the expected 7-substituted tetralones **7** and **8**, respectively, in excellent yields. Remarkably, Stille couplings with these heterocyclic stannanes occurred cleanly and rapidly, and little starting triflate remained after a few minutes. With these results in our hands, we decided to extend the Stille methodology to the coupling of triflate **5** with other



Scheme 1.

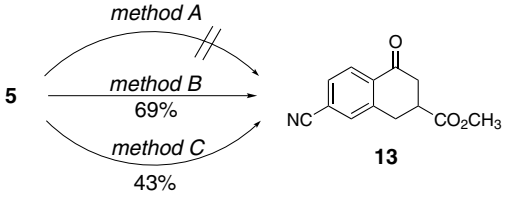
Table 1. Stille cross-coupling reactions of triflate **5**

Entry	Compound	R	Organotin	Catalyst (equiv)	Solvent	Time (h)	Yield (%)
1	**6**	Ph	$PhSnBu_3$	$Pd(PPh_3)_4$ (0.1)	Dioxane	18	86
2	**6**	Ph	$PhSnMe_3$	$Pd(PPh_3)_4$ (0.1)	Dioxane	9	87
3	**7**	2-Furyl	(2-Furyl)$SnBu_3$	$Pd(PPh_3)_4$ (0.2)	Dioxane	0.5	96
4	**8**	2-Thienyl	(2-Thienyl)$SnBu_3$	$Pd(PPh_3)_4$ (0.2)	Dioxane	3	96
5	**9**	H_2C=CH	(H_2C=CH)$SnBu_3$	$Pd(PPh_3)_4$ (0.1)	Dioxane	2	83
6	**10**	Ac	$Me_3Sn[C(OEt)=CH_2]$	$Pd(PPh_3)_4$ (0.1)	Dioxane	10	61
7	**10**	Ac	$Me_3Sn[C(OEt)=CH_2]$	$PdCl_2(PPh_3)_2$ (0.1)	DMF	22	78
8	**11**	HC≡C	(HC≡C)$SnBu_3$	$Pd(PPh_3)_4$ (0.1)	Dioxane	60	40

organostannanes. Tributyl(vinyl)tin (entry 5) yielded, after 2 h of reaction, the 7-vinyltetralone derivative (**9**) in 83% yield, whereas tributyl(1-ethoxyvinyl)tin underwent Stille coupling, yielding, after hydrolysis, the corresponding 7-acetyl derivative (**10**) in 61% overall yield (entry 6). This yield could be increased to 78% by using $PdCl_2(PPh_3)_2$ in DMF as the catalyst (entry 7).

When tributylstannylacetylene was used, after optimization of the experimental conditions, the corresponding 7-ethynyltetralone (**11**) was obtained in a moderate yield after 60 h (entry 8). This result prompted us to attempt the Sonogashira cross-coupling[14] to introduce the ethynyl substituent. Thus, reaction between triflate **5** and TMS–acetylene, using $Pd(PPh_3)_2Cl_2$ as the catalyst and CuI and triethylamine in DMF at 55 °C, yielded 7-ethynyl-4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (**12**) upon alkaline hydrolysis in 81% yield after 2 h of reaction.[15]

Cyanation reaction of triflate **5** was also assayed to obtain the corresponding aromatic nitrile **13**. The first reports in the literature that describe the metal-catalyzed displacement reaction of aryl triflates with sodium or potassium cyanide used nickel(0) as catalyst.[16] Application of this method (Scheme 2) on triflate **5** provided only the hydroxy derivative **4**. Later, the reagent system composed of zinc cyanide and catalytic $Pd(PPh_3)_4$ in DMF was reported to be a general and efficient system for cyanation of aryl triflates.[17] Under these conditions, using 10 mol % $Pd(PPh_3)_4$, triflate **5** was converted to nitrile **13** in 69% yield. Recently, Weissman et al. reported the successful ligand-free palladium-catalyzed cyanation of aryl halides[18] using $Pd(OAc)_2$ in combination with $K_4[Fe(CN)_6]$ as the cyanide source[19] in dimethylacetamide (DMAC). Under the same conditions, but using NMP as the solvent, triflate **5** was converted to nitrile **13** in 43% yield.[20] This, to our knowledge, is *the first example of ligand-free cyanation of an aryl triflate*.



Scheme 2. Cyanation conditions: method A: $NiCl_2(PPh_3)_2$, PPh_3, KCN, Zn dust, CH_3CN, reflux; method B: $Pd(PPh_3)_4$, $Zn(CN)_2$, DMF, 120 °C; method C: $Pd(OAc)_2$, $K_4[Fe(CN)_6]\cdot 3H_2O$, Na_2CO_3, NMP, 120 °C.

In summary, we have prepared a series of substituted tetralones via Pd-catalyzed cross-coupling reactions (Stille; Suzuki; Sonogashira) of 3-(methoxycarbonyl)-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl trifluoromethanesulfonate (**5**) with a variety of organometallic reagents. Triflate **5** can also undergo Pd-catalyzed cyanation in the presence of PPh_3 or in its absence (i.e., ligand-free). The use of these newly synthesized compounds as intermediates of novel CNS agents is currently in progress in our laboratory.

Acknowledgement

This work was supported by the Ministerio de Educación y Ciencia (Spain) under Grants SAF2002-04195-C03-01 and SAF2005-08025-C03-02. M. Torrado is grateful to the Ministerio de Educación y Ciencia for a predoctoral fellowship.

References and notes

1. Holstein, A. P.; Chen, C. H. *Am. J. Psychiatry* **1965**, *122*, 462–463.
2. King, D. J. *Eur. Neuropsychopharmacol.* **1998**, *8*, 33–42.
3. Capuano, B.; Crosby, I. T.; Lloyd, E. J. *Curr. Med. Chem.* **2002**, *9*, 521–548.
4. Melkersson, K.; Dahl, M.-L. *Drugs* **2004**, *64*, 701–723.
5. Raviña, E.; Masaguer, C. F. *Curr. Med. Chem.: Central Nervous System Agents* **2001**, *1*, 43–62.
6. Brea, J.; Rodrigo, J.; Carrieri, A.; Sanz, F.; Cadavid, M. I.; Enguix, M. J.; Villazón, M.; Mengod, G.; Caro, Y.; Masaguer, C. F.; Raviña, E.; Centeno, N. B.; Carotti, A.; Loza, M. I. *J. Med. Chem.* **2002**, *45*, 54–71.
7. Caro, Y.; Torrado, M.; Masaguer, C. F.; Raviña, E.; Padín, F.; Brea, J.; Loza, M. I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 585.
8. Alvarado, M.; Coelho, A.; Masaguer, C. F.; Raviña, E.; Brea, J.; Padín, F.; Loza, M. I. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3063.
9. Selected physical and spectral data for 3-(methoxycarbonyl)-1,2,3,4-tetrahydro-1-oxonaphthalen-6-yl trifluoromethanesulfonate (**5**): mp 80–81 °C (hexane). IR (KBr): 1725, 1688 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 2.81–3.01 (m, 2H); 3.21–3.26 (m, 3H); 3.72 (s, 3H); 7.22–7.25 (m, 2H); 8.13 (d, $J = 8.4$ Hz, 1H). MS (EI): $m/z = 352$ (M^+, 100%). Anal. Calcd for $C_{13}H_{11}F_3O_6S$ requires: C, 44.32; H, 3.15; S, 9.10. Found: C, 44.64; H, 3.08; S, 8.87.

10. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168; (c) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419–2440.
11. Different conditions were used in order to obtain the furyl and thienyl derivatives by Suzuki coupling: $Pd(PPh_3)_4$, $Cl_2Pd(PPh_3)_2$, or $Pd(OAc)_2$–S-Phos as catalyst; K_2CO_3 or Et_3N as the base, and DMF, toluene, or DME as the solvent.
12. (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636–3638; (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524; (c) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1–652.
13. Representative procedure for Stille cross-coupling reaction: preparation of methyl 4-oxo-7-phenyl-1,2,3,4-tetrahydronaphthalene-2-carboxylate (**6**): a mixture of triflate **5** (800 mg, 2.3 mmol), $PhSnBu_3$ (834 mg, 2.3 mmol), LiCl (289 mg, 6.8 mmol) and $Pd(PPh_3)_4$ (262 mg, 0.23 mmol) in dioxane (15 mL) was stirred at reflux temperature under argon for 18 h. After cooling, the solvent was evaporated under reduced pressure and the residue was dissolved in ether and washed with water and 10% HCl. The organic phase was dried (Na_2SO_4) and concentrated, and the resulting solid was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to give **6** (548 mg, 86%) as a white solid. Mp 109–110 °C (hexane). IR (KBr): 1734, 1684 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 2.81–3.01 (m, 2H); 3.23–3.31 (m, 3H); 3.74 (s, 3H); 7.40–7.58 (m, 4H); 7.60–7.63 (m, 3H); 8.01 (d, $J = 8.1$ Hz, 1H). MS (CI): $m/z = 281$ (MH^+, 100%). Anal. Calcd for $C_{18}H_{16}O_3 \cdot 1/5H_2O$ requires: C, 76.15; H, 5.82. Found: C, 76.10; H, 5.60. Selected physical and spectral data for Stille cross-coupling products: methyl 4-oxo-7-(2-furyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (**7**): mp 108–110 °C (toluene). IR (KBr): 1731, 1675 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 2.88–2.93 (m, 2H); 3.24–3.38 (m, 3H); 3.73 (s, 3H); 6.52 (dd, $J = 3.5$, 1.8 Hz, 1H); 6.80 (d, $J = 3.2$ Hz, 1H); 7.53 (d, $J = 1.2$ Hz, 1H); 7.57 (s, 1H); 7.61 (dd, $J = 8.2$, 1.5 Hz, 1H); 8.02 (d, $J = 8.2$ Hz, 1H). MS (CI): $m/z = 271$ (MH^+, 100%). Anal. Calcd for $C_{16}H_{14}O_4 \cdot 0.2Cl_2CH_2 \cdot 0.1C_6H_{14}$ requires: C, 68.20; H, 5.38. Found: C, 68.15; H, 5.47. Methyl 4-oxo-7-(2-thienyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (**8**): mp 120–122 °C. IR (KBr): 1727, 1686 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 2.79–2.99 (m, 2H); 3.19–3.27 (m, 3H); 3.74 (s, 3H); 7.12 (dd, $J = 5.0$, 3.7 Hz, 1H); 7.38 (dd, $J = 5.0$, 1.0 Hz, 1H); 7.43 (dd, $J = 3.6$, 0.9 Hz, 1H); 7.50 (s, 1H); 7.58 (dd, $J = 8.1$, 1.6 Hz, 1H); 8.03 (d, $J = 8.2$ Hz, 1H). MS (CI): $m/z = 287$ (MH^+, 100%). Anal. Calcd for $C_{16}H_{14}O_3S \cdot 1/5CH_2Cl_2 \cdot 1/4C_6H_{14}$ requires: C, 65.44; H, 5.55; S, 9.87. Found: C, 65.56; H, 5.27; S, 9.91. Methyl 4-oxo-7-vinyl-1,2,3,4-tetrahydronaphthalene-2-carboxylate (**9**): mp 82–83 °C (hexane). IR (KBr): 1728, 1673 cm^{-1}. ^1H NMR($CDCl_3$, 300 MHz): 2.71–2.97 (m, 2H); 3.17–3.21 (m, 3H); 3.74 (s, 3H); 5.40 (d, $J = 10.9$ Hz, 1H); 5.85 (d, $J = 17.6$ Hz, 1H); 6.72 (dd, $J = 10.9$, 7.4 Hz, 1H); 7.25 (s, 1H); 7.36 (d, $J = 8.0$ Hz, 1H); 8.00 (d, $J = 8.1$ Hz, 1H). MS (CI): $m/z = 231$ (MH^+, 100%). Anal. Calcd for $C_{14}H_{14}O_3 \cdot 0.1H_2O$ requires: C, 72.46; H, 6.17. Found: C, 72.67; H, 6.33. Methyl 4-oxo-7-acetyl-1,2,3,4-tetrahydronaphthalene-2-carboxylate (**10**): mp 97–98 °C (hexane). IR (KBr): 1726, 1683 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 2.63 (s, 3H); 2.83–3.01 (m, 2H); 3.20–3.31 (m, 3H); 3.72 (s, 3H); 7.85–7.88 (m, 2H); 8.10 (d, $J = 8.7$ Hz, 1H). MS (CI): $m/z = 247$ (MH^+, 85%). Anal. Calcd for $C_{20}H_{14}O_4 \cdot 0.15H_2O$ requires: C, 67.54; H, 5.79. Found: C, 67.58; H, 5.83.
14. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470; (b) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46–49; (c) Sonogashira, K. In *Cross-coupling reactions to sp carbon atoms*; Diederich, F., Stang, P. J., Eds.; Metal-Catalyzed Cross-Coupling Reactions; Wiley-VCH: Weinheim, 1998; pp 203–229.
15. Selected physical and spectral data for 7-ethynyl-4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (**12**): mp 200–202 °C (benzene). IR (KBr): 3283, 1700, 1674 cm^{-1}. ^1H NMR (CD_3OD, 300 MHz): 2.89–2.95 (m, 2H); 3.19–3.35 (m, 3H); 3.78 (s, 1H); 7.36–7.49 (m, 2H); 7.94 (d, $J = 8.0$ Hz, 1H). MS (CI): $m/z = 407$ (MH^+, 86%). Anal. Calcd for $C_{13}H_{10}O_3 \cdot 0.05H_2O$ requires: C, 72.58; H, 4.73. Found: C, 72.46; H, 4.79.
16. (a) Takagi, K.; Sakakibara, Y. *Chem. Lett.* **1989**, 1957–1958; (b) Chambers, M. R. I.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1365–1366; (c) Almansa, C.; Carceller, E.; Bartroli, J.; Forn, J. *Synth. Commun.* **1993**, *23*, 2965–2971.
17. (a) Selnick, H. G.; Smith, G. R.; Tebben, A. J. *Synth. Commun.* **1995**, *25*, 3255–3261; (b) Kubota, H.; Rice, K. C. *Tetrahedron Lett.* **1998**, *39*, 2907–2910.
18. Weissman, S. A.; Zewge, D.; Chen, C. *J. Org. Chem.* **2005**, *70*, 1508–1510.
19. Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 1388–1389.
20. Selected physical and spectral data for methyl 7-cyano-4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (**13**): mp 159–160 °C (hexane). IR (KBr): 2240, 1710, 1689 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 2.85–2.97 (m, 2H); 3.01–3.26 (m, 3H); 3.72 (s, 3H); 7.58–7.36 (m, 2H); 8.11 (d, $J = 8.7$ Hz, 1H). MS (CI): $m/z = 230$ (MH^+, 9%). Anal. Calcd for $C_{13}H_{11}NO_3 \cdot 0.35H_2O$ requires: C, 66.29; H, 5.01; N, 5.95. Found: C, 66.30; H, 4.81; N, 5.84.