A General and Facile Synthesis of 1,3-Diaryl-4-pyrazoleacetic Acid Esters#

David D. Xu, George T. Lee, Xinglong Jiang, Kapa Prasad,*
Oljan Repic and Thomas J. Blacklock

Chemical and Analytical Development, Novartis Institute for Biomedical Research, East Hanover, New Jersey 07936, USA

Received May 12, 2004

A general synthesis of 1,3-diaryl-4-pyrazoleacetic acid esters has been realized *via* the condensation of a γ-carboxy ester hydrazone with the Vilsmeier reagent.

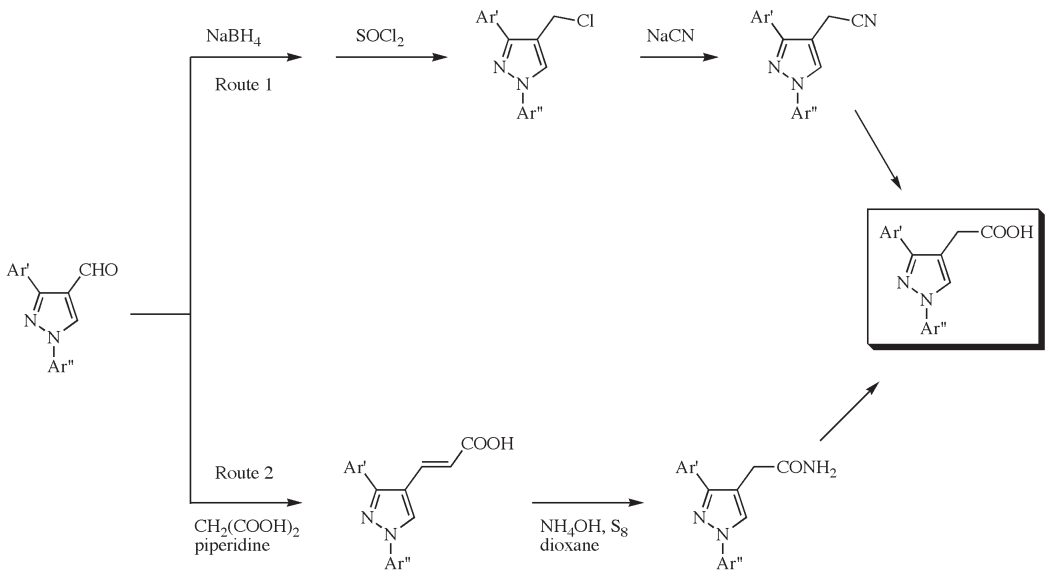
J. Heterocyclic Chem., **42**, 131 (2005).

1,3-Diaryl-4-pyrazoleacetic acids and derivatives exhibit multiple biological activities [1]. For example, Lonazolac® is listed in Merck Index as an anti-inflammatory and analgesic agent [1a]. To support our pre-clinical study and the drug development program, we needed an efficient and readily scalable procedure for making this class of compounds. However, despite the fact that 1,3-diaryl-4-pyrazoleacetic acids and derivatives had been known for a long time, there was, to our knowledge, only one method reported for making them. The preparation invariably involved a one-carbon homologation of the corresponding 1,3-diaryl-4-pyrazolecarboxaldehyde [1,2]. This one-carbon homologation was accomplished *via* either the cyanide route or the Willgerodt degradation [3] route (Scheme 1). However, both of these routes suffered various drawbacks, particularly for large-scale preparation. The high toxicity of sodium cyanide and the instability of the intermediate chloride impeded the first choice for scaling up. On the other hand, the degradation conditions in the second choice were too corrosive and required high temperature and high pressure [3]. Both methods are lengthy and inefficient. We report in this letter a new synthetic route, which offers an expedient access to the title compounds. The method is also readily adaptable for large-scale preparations.

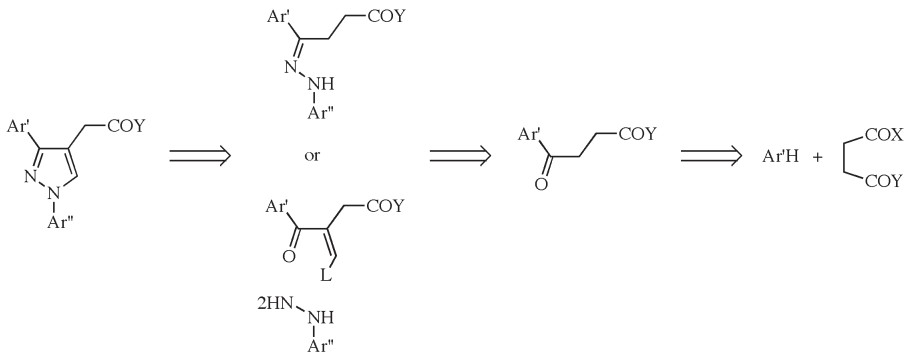
Since all the drawbacks associated with the known method arose from the one-carbon extension of the carboxyaldehyde, in the new design we opted to build the pyrazole ring on a "correct" carbon framework (Scheme 2). We envisaged that the pyrazole core could be constructed *via* either a hydrazone intermediate or a 1,3-dicarbonyl derivative. Both of these intermediates can be obtained from the corresponding γ-keto carboxylic acid derivative, a Friedel-Crafts acylation product between an appropriate arene and a succinic acid derivative.

The well documented condensation [4] of the 1,3-dicarbonyl derivative and arylhydrazines were investigated first. While formylation of the γ-keto ester under normal conditions (LDA, HCOOEt) did not give the desired 1,3-dicarbonyl product cleanly, the β-enaminone can be obtained in almost quantitative yield when the γ-keto ester was reacted with dimethylformaide dimethyl acetal in toluene under reflux [5]. Unfortunately the "wrong" regioisomer, 1,5-diaryl-4-pyrazole acetic acid, was formed

Scheme 1



Scheme 2



Alternative Synthetic Design

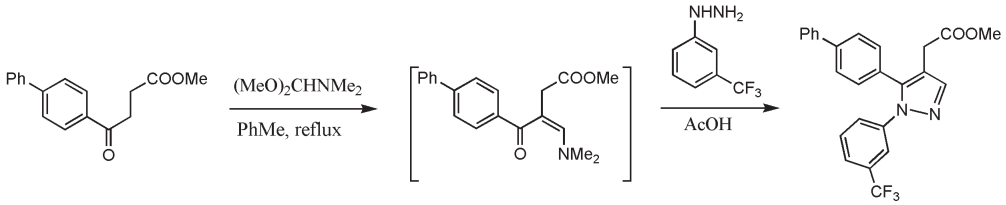


Figure 1

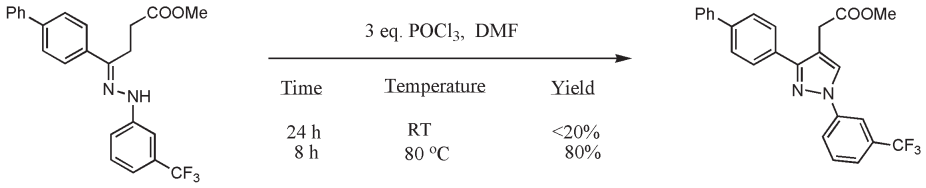


Figure 2

predominantly (and sometimes exclusively) when the β-enaminone was reacted with an arylhydrazine (Figure 1).

The condensation of γ-hydrazone esters and the *in situ* generated Vilsmeier reagent afforded the pyrazole of desired regiochemistry (Figure 2). Although the reaction was very sluggish at room temperature, which proceeded to only 20% conversion after 24 h, the condensation proceeded smoothly at 80 °C and went to completion (80% yield) in 8 h.

The method is general and is applicable to a variety of substrates (Table). The electronic effect from aryl groups has very little influence on the condensation, attested by comparable ring closing rates from both electron deficient and electron rich aromatic groups. However, bulky esters (*i.e.* isopropyl esters) have to be applied for the formation of the corresponding hydrazone from electron rich arylhydrazines. The intramolecular cyclization [6] otherwise becomes the predominating pathway (Figure 3). For the same reason, alkylhydrazines did not form stable hydrazone esters. While the remote ester group does not influence this pyrazole ring formation (Figure 4), the free acid or the amide groups react with the Vilsmeier reagent thus interfering with the condensation.

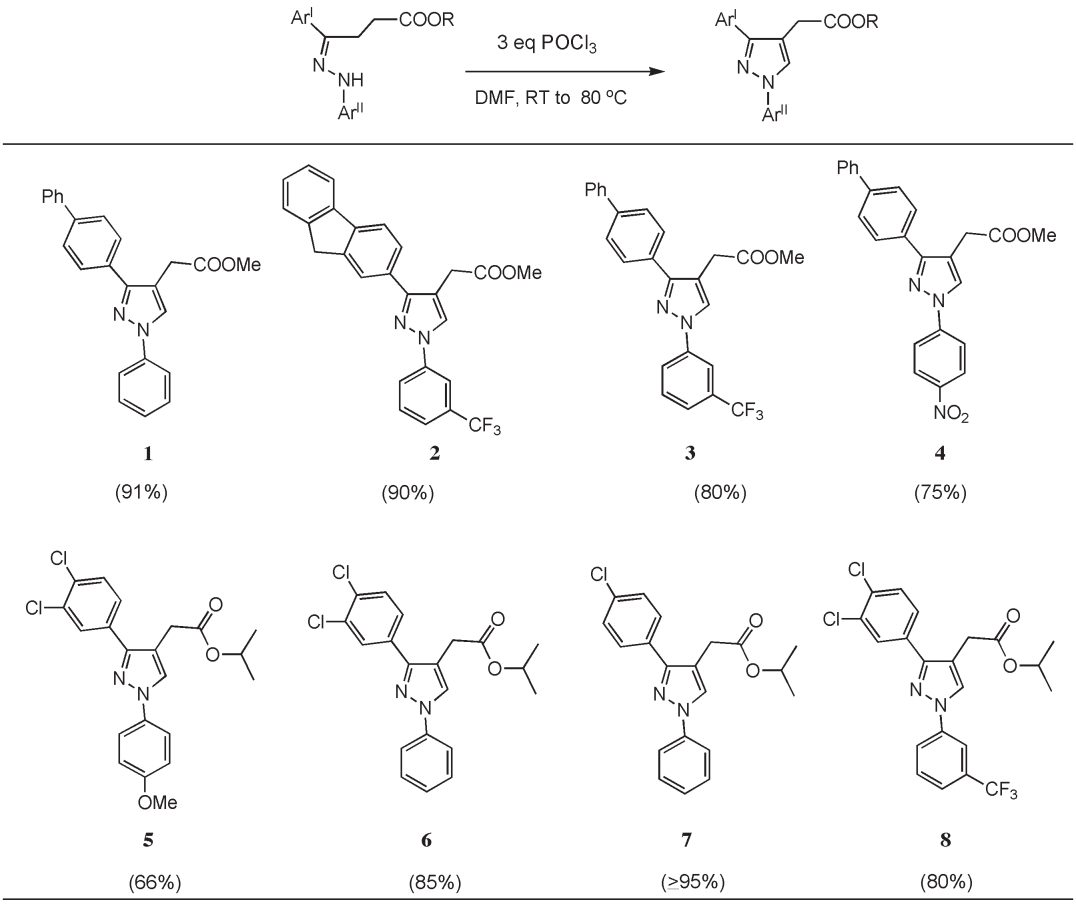
In conclusion, we have found a concise and general method for the formation of 1,3-diaryl pyrazole-4-acetic acids and their derivatives. The method has been successfully applied to the synthesis of one of our drug substances on multi-kilograms scale. The simplicity of the method should facilitate further investigation of this class of biologically interesting compounds in greater detail.

EXPERIMENTAL

Representative Procedure.

To a solution of 1.0 L of dimethylformamide was added over a period of 45 min 230.0 g (1.5 mol) of phosphorus oxychloride at 0 °C. After 30 min at 0 °C, 213.22 g (0.50 mol) of the hydrazone, 4-[1,1'-biphenyl]-γ-[3-trifluoromethylphenyl]hydrazono-butanoic acid methyl ester, was added as a solid. The solution was heated at 80 °C for 10 h. The reaction was quenched at room temperature with water (1.0 L, *exothermic!*). The product was extracted into a mixture of 2 L of 1:2

Table



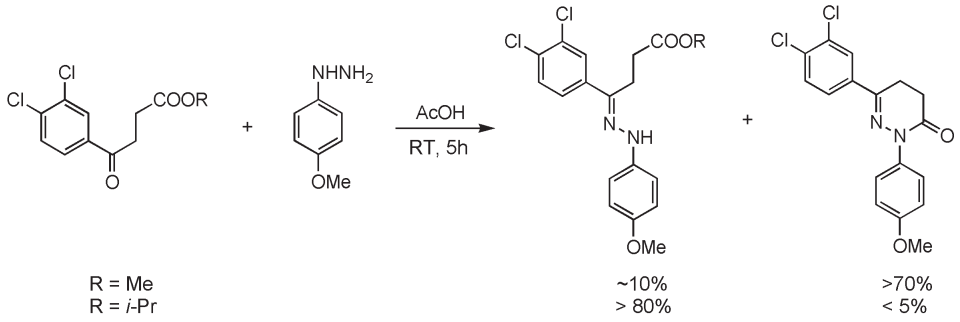


Figure 3

ethyl acetate and heptane. The organic layer was washed in sequence, with 0.5 L of 2 *N* HCl aqueous solution, 0.5 L of water and 0.5 L of 2 *N* NaOH aqueous solution. The organic layer was filtered through a silica gel pad (250 g) and the pad washed with 1.5 L of 1:1 heptane and ethyl acetate. The combined organic layer was concentrated to about 1.0 L and cooled at 20 °C for 2 h. The product, 3-[1,1'-biphenyl]-4-yl-1-[3-(trifluoromethyl)-phenyl]-1*H*-pyrazole-4-acetic acid methyl ester (**3**), was collected by filtration as a white powder (180 g, 82.5%).

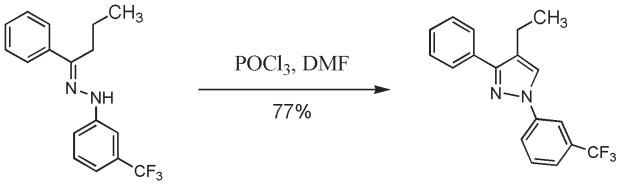


Figure 4

Methyl 3-(1,1'-Biphenyl)-4-yl-1-phenyl-1*H*-pyrazole-4-acetate (**1**).

Compound **1** was obtained as a pale yellow solid (91% yield); mp 116-117 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.74 (3H, s), 3.76 (2H, s), 7.28-7.30 (1H, t, J=7 Hz), 7.35-7.38 (1H,t, J=7 Hz); 7.44-7.48 (4H, t, J=8 Hz), 7.64-7.70 (4H, dd, J=7 Hz), 7.76-7.78 (4H, d, J=7 Hz), 8.0 (1H, s). ^{13}C NMR (500 MHz, $CDCl_3$): δ 172.06, 151.77, 140.88, 140.13, 132.16, 129.54, 128.98, 128.58, 128.07, 127.56, 127.46, 127.22, 126.52, 119.08, 113.32, 52.34, 30.49; MS (ESI, m/z) 368 (M^+).

Anal. Calcd for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60; O, 8.69. Found: C, 78.43; H, 5.69; N, 7.53.

Methyl 3-(9*H*-Fluoren-2-yl)-1-[3-(trifluoromethyl)phenyl]-1*H*-pyrazole-4-acetate (**2**).

Compound **2** was obtained as a pale yellow solid (90% yield); mp 109-110 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.74 (3H, s), 3.77 (2H, s), 3.98 (2H, s), 7.31-7.34 (1H, t, J=7 Hz), 7.38-7.40 (1H,t, J=7 Hz); 7.52-7.58 (3H, m, J=8 Hz), 7.66-7.68 (1H, d, J=8 Hz), 7.82-7.83 (1H, d, J=7 Hz), 7.86-7.89 (2H, t, J= 8 Hz). 7.95-7.97 (1H, d, J= 8 Hz), 8.07 (1H, s), 8.12 (1H, s). ^{13}C NMR (500 MHz, $CDCl_3$): δ 171.90, 153.22, 143.86, 141.98, 141.41, 140.42, 132.59, 132.26, 131.93, 131.61, 131.08, 130.16, 127.95, 126.97, 126.94, 125.23, 124.88, 122.87, 122.80, 122.51, 121.79, 120.23, 120.11, 115.85, 115.82, 115.78, 115.74, 114.13, 52.36, 37.12, 30.43; MS (ESI, m/z) 448 (M^+).

Anal. Calcd for $C_{26}H_{19}F_3N_2O_2$: C, 69.64; H, 4.27; N, 6.25; F, 12.71; O, 7.14. Found: C, 69.49; H, 4.29; N, 6.25.

Methyl 3-(1,1'-Biphenyl)-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-4-acetate (**3**).

Compound **3** was obtained as a pale yellow solid (80% yield); mp 109-110 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.74 (3H, s), 3.76 (2H, s), 7.35-7.38 (1H, t, J=7 Hz), 7.45-7.48 (2H,t, J=7 Hz); 7.52-7.59 (2H, t, J=8 Hz), 7.63-7.65 (2H, d, J=7 Hz), 7.69-7.70 (2H, d, J=7 Hz), 7.76-7.78 (2H, d, J=8 Hz), 7.94-7.96 (1H, d, J=8 Hz), 8.06 (1H, s) , 8.12 (1H, s). ^{13}C NMR (500 MHz, $CDCl_3$): δ 171.87, 152.50, 141.20, 140.76, 140.39, 132.26, 1431.93, 131.67, 130.18, 128.98, 128.58, 127.98, 127.63, 127.51, 127.21, 125.21, 122.92, 122.89, 122.50, 121.79, 115.81, 115.77, 114.14, 52.40, 30.37; MS (ESI, m/z) 436 (M^+).

Anal. Calcd for $C_{25}H_{19}F_3N_2O_2.1.2\%H_2O$: C, 67.96; H, 4.47; N, 6.34; F, 12.90; O, 8.33. Found: C, 67.78; H, 4.64; N, 6.26.

Methyl 3-(1,1'-Biphenyl)-1-(4-nitrophenyl)-1*H*-pyrazole-4-acetate (**4**).

Compound **4** was obtained as a pale yellow solid (75% yield); mp 174-175 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.76 (3H, s), 3.78 (2H, s), 7.36-7.408 (1H, t, J=7 Hz), 7.46-7.49 (2H,t, J=7 Hz); 7.64-7.66 (2H, d, J=8 Hz), 7.70-7.72 (2H, d, J=8 Hz), 7.76-7.78 (2H, d, J=8 Hz), 7.94-7.96 (2H, d, J=9 Hz), 8.20 (1H, s) , 8.33-8.35 (2H, d, J=9 Hz)). ^{13}C NMR (500 MHz, $CDCl_3$): δ 169.89, 151.78, 143.63, 142.53, 139.77, 138.85, 129.50, 127.28, 126.81, 126.51, 126.00, 125.82, 125.46, 123.75, 116.57, 113.58, 50.74, 28.58; MS (ESI, m/z) 413 (M^+).

Anal. Calcd for $C_{24}H_{19}N_3O_4$: C, 69.72; H, 4.63; N, 10.16; O, 15.48. Found: C, 69.71; H, 4.64; N, 10.08.

Isopropy 3-(3,4-Dichlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrazole-4-acetate (**5**).

Compound **5** was obtained as a pale yellow viscous oil (66% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23 (6H, s), 3.63 (2H, s), 3.84 (3H, s), 5.03-5.06 (m, 1H), 6.96-6.98 (2H, d, J=7 Hz), 7.49-7.50 (1H,d, J=7 Hz); 7.55-7.56 (dH, d, J=8 Hz), 7.61-7.63 (2H, d, J=8 Hz), 7.85 (1H, s), 7.93 (1H, s). ^{13}C NMR (500 MHz, $CDCl_3$): δ 170.80, 158.53, 149.23, 133.66, 133.46, 132.76, 131.95, 130.57, 129.83, 128.40, 127.26, 120.81, 114.65, 113.19, 68.86, 55.69, 30.93, 21.88; MS (ESI, m/z) 419 (M^+).

Anal. Calcd for $C_{21}H_{20}Cl_2N_2O_3$: C, 60.15; H, 4.81; N, 6.68; Cl, 16.91; O, 11.45. Found: C, 60.01; H, 4.79; N, 6.40; Cl, 17.21.

Isopropy 3-(3,4-Dichlorophenyl)-1-phenyl-1H-pyrazole-4-acetate (**6**).

Compound **6** was obtained as a pale yellow viscous oil (85% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (6H, s), 3.64 (2H, s), 5.03-5.06 (1H, m), 7.29-7.32 (1H, t, J=7 Hz), 7.44-7.51 (3H, m,); 7.57-7.59 (1H, d, J=8 Hz), 7.72-7.74 (2H, d, J=8 Hz), 7.85 (1H, s), 7.93 (1H, s). ^{13}C NMR (500 MHz, $CDCl_3$): δ 169.54, 148.52, 138.71, 132.19, 131.64, 130.94, 129.44, 128.70, 128.46, 128.41, 128.38, 127.15, 126.12, 125.63, 117.96, 117.93, 112.50, 67.74, 29.78, 20.72; MS (ESI, m/z) 389 (M^+).

Anal. Calcd for $C_{20}H_{18}Cl_2N_2O_2$: C, 61.71; H, 4.66; N, 7.20; Cl, 18.21; O, 8.22. Found: C, 61.42; H, 4.60; N,6.90; Cl, 18.58.

Isopropy 3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazole-4-acetate (**7**).

Compound **7** was obtained as a pale yellow viscous oil (95% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23 (6H, s), 3.64 (2H, s), 5.01-5.05 (1H, m), 7.25-7.31 (1H, t, J=7 Hz), 7.40-7.43 (4H, dd, J= 8 Hz), 7.64-7.75 (4H, dd, J=8 Hz), 8.03 (1H, s). ^{13}C NMR (500 MHz, $CDCl_3$): δ 170.88, 150.89, 140.02, 134.06, 131.77, 129.54, 129.49, 129.48, 129.44, 128.89, 128.86,128.08, 126.59, 119.06, 113.52, 68.73, 30.97, 21.87; MS (ESI, m/z) 354 (M^+).

Anal. Calcd for $C_{20}H_{19}ClN_2O_2$: C, 67.70; H, 5.40; N, 7.89; Cl, 9.99; O, 9.02. Found: C, 67.51, H, 5.39; N, 7.67; Cl, 9.90.

Isopropy 3-(3,4-Dichlorophenyl)-1-[3-(trifluoromethyl)phenyl]-1*H*-pyrazole-4-acetate (**8**).

Compound **8** was obtained as a white solid (80% yield); mp 105-106 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (6H, s), 1.65 (2H, s), 5.03-5.06 (1H, m), 7.52-7.60 (4H, m,); 7.85 (1H, s), 7.92-7.94 (1H, d, J= 8 Hz), 8.02 (1H, s), 8.10 (1H, s). ^{13}C NMR (500 MHz, $CDCl_3$): δ 169.97, 149.88, 139.59, 132.36, 132.30, 131.92, 131.78, 131.45, 130.13, 129.68, 127.70, 126.74, 124.53, 122.70, 122.67, 122.63, 122.59, 121.83, 121.29, 115.34, 115.30, 115.26, 115.23, 113.89, 68.50, 30.26, 21.30; MS (ESI, m/z) 457 (M^+).

Anal. Calcd for $C_{21}H_{17}Cl_2F_3N_2O_2$: C, 55.16; H, 3.75; N, 6.13; F, 12.46; Cl, 15.51; O, 7.00. Found: C, 55.37; H, 3.65; N, 6.00; Cl, 15.57.

6-(3,4-Dichlorophenyl)-2-(4-methoxyphenyl)-4,5-dihydro-3(2*H*)-pyridazinone (**9**).

Compound **9** was obtained as a beige solid (60% yield); mp 104-105 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.73-2.77 (2H, t, J= 7 Hz)), 2.98-3.01 (2H, t, J= 7 Hz). 3.81 (3H, s), 6.93-6.60 (2H, d, J= 8 Hz), 7.41-7.48 (3H, m,); 7.59-7.61 (1H, d, J= 8 Hz), 7.87 (1H, s). ^{13}C NMR (500 MHz, $CDCl_3$); δ 165.06, 158.47, 148.68, 135.55, 134.22, 134.08, 133.17, 130.66, 127.99, 126.59, 125.25, 114.05, 55.63, 27.75, 22.84; MS (ESI, m/z) 349 (M^+).

Anal. Calcd for $C_{17}H_{14}Cl_2N_2O_2$: C, 58.47; H, 4.04; N, 8.02; Cl, 20.30; O, 9.16. Found: C, 58.34; H, 4.11; N, 7.82; Cl, 20.15.

REFERENCES AND NOTES

Part of this material was presented at the "Fifth North American Chemical Congress" Cancun, Mexico, 1997, and at the "215th ACS National Meeting", Dallas, USA, 1998.

* Corresponding author. E-mail: prasad.kapa@pharma.novartis.com.

[1a] R. Von Riedel,. *Arzneim.-Forsch./Drug Res.*, **31**, 655 (1996); [b] G. Rainer, U. S. Patent 4,146,721 (1979), and U. S. Patent 4,325,962 (1982), Byk-Gulden Lomberg Chemische Fabrik GmbH.

[2] M. A. Kira, M. N. Aboul-Enein and M. I. Korkor, *J. Heterocyclic Chem.* **7**, 25 (1970).

[3] Willgerodt degradation: M. Carmack and M. A. Speilman. *Organic Reactions*, Vol. **3**, pp 83 (1946).

[4a] C. Chen, K. Wilcoxen and J. R. McCarthy. *Tetrahedron Lett.* **39**, 8229 (1998); [b] M. M. Curzu, G. A. Pinna, D. Barlocco and G. Cignarella, *J. Heterocyclic Chem.* **27**, 205 (1990); [c] A. Alberola, C. Andres, O.A. Gonzalez, R. Pedrosa and M. Vicente, *An. Quim., Ser. C* **83**, 55 (1987); [d] S. P. Singh, R. K. Vaid, I. Prakash and O. Prakash, *Indian J. Chem., Sect. B* **25B**, 945 (1986); [e] E. C. Taylor and F. Sowinski, *J. Am. Chem. Soc.*, **90**, 1374 (1968).

[5] P. F. Schuda, C. B. Ebner and T. M. Morgan, *Tetrahedron Lett.* **27**, 2567 (1986).

[6] M. S. Y. Khan and A. A. Siddiqui, *Indian J. Chem., Sect. B* **39B**, 614 (1986).