The Reaction of 3,4-Dihydroisoquinolines With Malonic Acid and Its Derivatives

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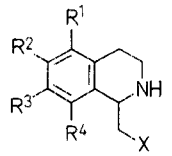
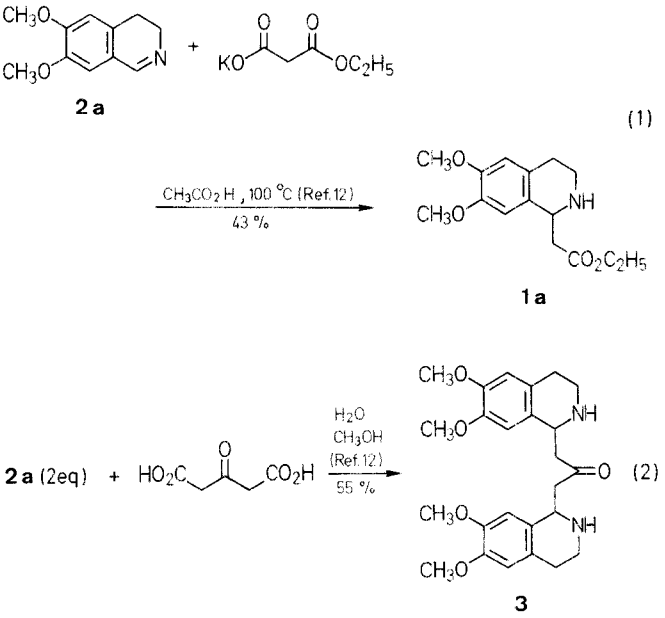
The reaction of various 3,4-dihydroisoquinolines with malonic acid gives the corresponding 1,2,3,4-tetrahydro-1-isoquinolineacetic acids in good yield, while the reaction with cyanoacetic acid and malonic acid half ethyl ester affords 1,2,3,4-tetrahydro-1-isoquinoline acetonitriles and 1,2,3,4-tetrahydro-1-isoquinolineacetic esters respectively. The use of other 1,3-dicarbonyls which cannot decarboxylate in this reaction affords the normal addition products.

During the past four decades the amino acids, esters and nitriles of the type **1** have been employed as intermediates for the synthesis of various nitrogenous substances of both natural and man-made origin.[1-9] To date, however, the methods for obtaining these bases have been plagued by various drawbacks.[4,7,10-12] Low yields, little or no generality, or tedious reaction sequences associated with preparing **1** have resulted in their limited usefulness as readily accessible synthetic intermediates.



1 X = CO_2H, $CO_2C_2H_5$, CN

We wish to report here a simple, general synthesis of these bases starting from readily available 3,4-dihydroisoquinolines. Chapman et al. found that the reaction of 6,7-dimethoxy- 3,4-dihydroisoquinoline **2a** with the potassium salt of the monoethyl ester of malonic acid afforded a 43% yield of the amino ester **1a** (eq. 1).[12] The same type of reaction occured when two equivalents of **2a** were reacted with acetone dicarboxylic acid to give **3** in 55% yield (eq. 2).[12] Several years later Jacquet reported the formation of the aminonitrile **1b** in 58% yield when **2a** was reacted with potassium cyanoacetate in hot acetic acid (eq. 3).[5] No further work, however, has been published in this area.



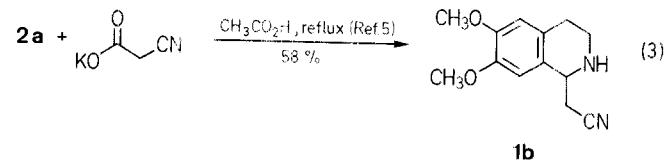
2a (1) CH_3CO_2H, 100 °C (Ref. 12), 43% → **1a**

2a (2eq) + HO_2C–CO–CO_2H (H_2O, CH_3OH, (Ref. 12), 55%) → **3** (2)

Table 1. Compounds **1a–m** Prepared

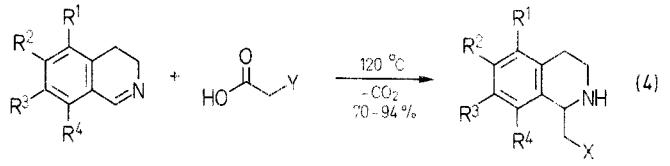
Substrate	Product	Y	R^1	R^2	R^3	R^4	Yield[a] (%)	m.p. (°C)[b]	Molecular Formula[c] or Lit. m.p. (°C)	IR (KBr)[d] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$)[e] δ (ppm)	MS[f] *m/e* (%)
2a	**1a**	$CO_2C_2H_5$	H	OCH_3	OCH_3	H	81	73–74	77–78[10]	3440, 1720	1.27 (t, 3H, J = 7.1 Hz); 2.64–3.27 (m, 6H); 3.84 (s, 3H); 3.85 (s, 3H); 4.20 (q, 2H, J = 7.1 Hz); 4.40 (dd, 1H, J = 9.1, 3.8 Hz); 6.59 (s, 2H)	279 (5), 192 (100)
2a	**1b**	CN	H	OCH_3	OCH_3	H	70	118–119	120[5]	3390, 2260	2.59–2.83 (m, 4H); 2.97–3.25 (m, 2H); 3.86 (s, 6H); 4.32 (t, 1H, J = 6.5 Hz); 6.57 (s, 1H); 6.60 (s, 1H)	232 (3), 192 (100)
2a	**1c**	CO_2H	H	OCH_3	OCH_3	H	92	251–252	$C_{13}H_{17}NO_4$ (251.3)	2450, 1570	–	251 (2), 192 (100)
2b	**1d**	$CO_2C_2H_5$	OCH_3	OCH_3	OCH_3	H	86	oil	$C_{16}H_{23}NO_5$ (309.4)	3300, 1710[g]	1.28 (t, 3H, J = 7.1 Hz); 2.63–3.24 (m, 6H); 3.85 (s, 6H); 4.19 (s, 3H); 4.38 (dd, 1H, J = 8.8, 4.5 Hz); 6.40 (s, 1H)	309 (90), 222 (100)
2b	**1e**	CN	OCH_3	OCH_3	OCH_3	H	82	101–102	$C_{14}H_{18}N_2O_3$ (262.3)	3400	2.62–3.19 (m, 6H); 3.84 (s, 3H); 3.86 (s, 6H); 4.30 (t, 1H, J = 6.5 Hz); 6.41 (s, 1H)	262 (3), 222 (100)
2b	**1f**	CO_2H	H	OCH_3	OCH_3	H	83	223–224	$C_{14}H_{19}NO_5$ (281.3)	2900, 1580	–	281 (2), 222 (100), 206 (76)
2c	**1g**	$CO_2C_2H_5$	H	OCH_3	OH	H	87	103–104	$C_{14}H_{19}NO_4$ (265.3)	3400, 3100, 1750	2.60–3.27 (m, 6H); 3.85 (s, 3H); 4.18 (q, 2H, J = 7.1 Hz); 4.34 (dd, 1H, J = 9.4, 2.7 Hz); 6.55 (s, 1H); 6.64 (s, 1H)	265 (9), 178 (100)
2c	**1h**	CN	H	OCH_3	OH	H	84	171–174	$C_{12}H_{14}N_2O_2$ (218.3)	3350, 2700, 2250	2.60–3.27 (m, 6H); 3.86 (s, 3H); 4.27 (t, 1H, J = 6.8 Hz); 6.58 (s, 1H); 6.61 (s, 1H)	218 (3), 178 (100)
2c	**1i**	CO_2H	H	H	H	H	81	>260	$C_{12}H_{15}NO_4$ (237.3)	3000, 1560	–	237 (18), 163 (100)
2d	**1j**	$CO_2C_2H_5$	H	H	H	H	93	oil	$C_{13}H_{17}NO_2$ (219.3)	3350, 1730[g]	1.29 (t, 3H, J = 7.1 Hz); 2.70–3.27 (m, 6H); 4.19 (q, 2H, J = 7.1 Hz); 4.46 (dd, 1H, J = 9.6, 3.1 Hz); 7.05–7.25 (m, 4H)	219 (90), 190 (67)
2d	**1k**	CO_2H	H	H	H	H	94	oil	$C_{11}H_{12}N_2$ (172.2)	3250, 2220[g]	2.75–3.23 (m, 6H); 4.39 (t, 1H, J = 6.4 Hz); 7.01–7.18 (m, 4H)	172 (1), 132 (100)
2d	**1l**	CO_2H	H	H	H	H	88	244–245	$C_{11}H_{13}NO_2$[h] (191.2)	2680, 1575	–	191 (3), 132 (100)
2d	**1m**	$CO_2C_2H_5$	H	OCH_3	OH	NO_2	73	159	159[g]	2400, 1710, 1510	1.27 (t, 3H, J = 7.1 Hz); 2.45–3.25 (m, 6H); 3.92 (s, 3H); 4.16 (q, 2H, J = 7.1 Hz); 4.92 (d, 1H, J = 7.0 Hz); 6.75 (s, 1H)	223 (100)

[a] Yields of isolated pure material.
[b] Uncorrected, recorded on a Thomas-Hoover capillary apparatus.
[c] Satisfactory microanalyses obtained: C ±0.35, H ±0.27, N ±0.26.
[d] Recorded on a Perkin-Elmer 137 spectrophotometer.
[e] Recorded on a Bruker WM-250 (250 MHz) instrument.
[f] Recorded on a Perkin-Elmer 270B spectrometer.
[g] Measured as film.
[h] No physical data is reported for this compound in Ref. 19.



(3)

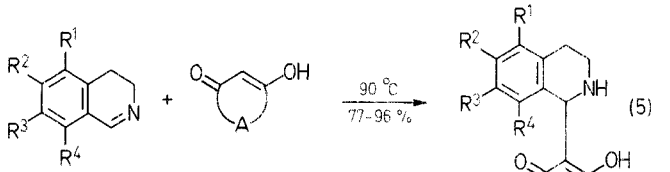
After several attempts on our part of optimize the yields of the above reactions we found that a neat mixture of the 3,4-dihydroisoquinoline **2a** and two equivalents of malonic acid half ethyl ester reacted at elevated temperature (120 °C) to afford an excellent yield (81%) of **1a**. Likewise, when cyanoacetic acid (two equivalents) and malonic acid (one equivalent) were substituted for the malonic ester the products **1b** (70%) and **1c** (92%) were obtained, respectively. The results of this reaction (eq. 4) involving various 3,4-dihydroisoquinolines as starting materials are shown in Table 1. An extension of this procedure to include 1-alkyl-3,4-dihydroisoquinolines as starting materials failed to give the expected product. Complete recovery of the dihydroisoquinoline resulted.



2a-e **1a-m**

(4)

A successful extension of this procedure was achieved, however, when other 1,3-dicarbonyl compounds which cannot decarboxylate was substituted as the nucleophilic species.[17] Thus, when a neat mixture of 5,6,7-trimethoxy-3,4-dihydroisoquinoline **2b** and one equivalent of β-tetronic acid[18] were heated to 90 °C an 89% yield of **4a** was obtained (eq. 5). Similar results were obtained when cyclohexane 1,3-dione and dimedone were employed as the nucleophiles (Table 2). As in the case above, however, extension of this reaction to include 1-alkyl-3,4-dihydroisoquinolines as starting materials failed and only the dihydroisoquinolines were recovered.



2a,b,d **4a-c**

(5)

In summary, 1,2,3,4-tetrahydro-1-isoquinoline acetates and nitriles are easily obtained by reacting the corresponding 3,4-dihydroisoquinolines with malonic acid, malonic acid half ethyl ester or cyanoacetic acids. This reaction also works well when 1,3-dicarbonyls which cannot decarboxylate are employed as the nucleophilic compounds. Neither reaction, however, affords products when 1-alkyl-3,4-dihydroisoquinolines are employed as the starting materials. This method allows easy access to the important intermediates of the type **1**.

3,4-Dihydroisoquinolines **2a, c, d** and **e** were obtained by literature procedures.[9,13–15]

5,6,7-Trimethoxy-3,4-dihydroisoquinoline (2b):

To a solution of 5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline[16] (10.0 g, 44.8 mmol) in dichloromethane (200 ml) at 0 °C is added N-bromosuccinimide (8.7 g, 49.3 mmol) portionswise over 20 min. After stirring for 30 min at 0 °C, 30% aqueous sodium hydroxide solution (50 ml) is added and the mixture is stirred for an additional 60 min at 25 °C. The organic layer is separated and washed with water (100 ml). The product is extracted from the organic layer with 10% aqueous hydrochloric acid (4 × 100 ml) and the combined acidic layer is washed with dichloromethane (100 ml). The acidic layer is made basic with concentrated ammonia (pH = 9) and the liberated base is extracted with dichloromethane (3 × 100 ml). The combined organic layer is dried with sodium sulfate and the solvent is evaporated *in vacuo* to give a yellow oil. Purification of the crude base on silica gel (ethyl acetate) affords **2b** as a colorless oil; yield: 7.9 g (78%).

^{1}H-NMR ($CDCl_3$): δ = 2.68 (t, 2H, J = 7.8 Hz); 3.72 (td, 2H, J = 7.8, 2.0 Hz); 3.86 (s, 3H); 3.88 (s, 3H); 3.91 (s, 3H); 6.65 (s, 1H); 8.22 ppm (t, 1H, J = 2.0 Hz)

MS: m/e = 232 (M^+, 100%).

The base **2b** is converted to its hydrochloride by dropwise addition of concentrated hydrochloric acid to a solution of **2b** (1.09 g) in ice cold tetrahydrofuran (100 ml). The precipitate is filtered and recrystallized from methanol-acetone; m.p. 149–151 °C.

$C_{12}H_{16}ClNO_3$	calc.	C 55.92	H 6.26	N 5.44	Cl 13.76
(257.7)	found	55.64	6.40	5.18	13.83

IR (KBr): ν = 2800, 1650

Synthesis of β-Amino Acids 1c,f,i and l from 3,4-Dihydroisoquinolines and Malonic Acid; General Procedure:

The dihydroisoquinoline (5.0 mmol) and malonic acid (5.0 mmol) are mixed well at 25 °C. The mixture is immersed in an oil bath preheated to 120 °C. After 30–60 min of intermittant manual stirring gas evolution ceases. The light brown solid residue is recrystallized directly from aqueous methanol to afford the amino acids **1** as colorless, analytically pure needles (Table 1).

Synthesis of β-Amino Esters and β-Amino Nitriles 1a,b,d,e,g,h,j,k and m from 3,4-Dihydroisoquinolines and Malonic Acid Half Ethyl Ester and Cyanoacetic Acid, Respectively; General Procedure:

The dihydroisoquinoline (5.0 mmol) and malonic acid half ethyl ester (5.0 mmol; cyanoacetic acid in the case of β-amino nitriles) are mixed well at 25 °C and then inserted into an oil bath preheated to 120 °C (in some cases the reaction begins to take place upon mixing). After 30–60 min of intermittant manual stirring gas evolution ceases. The resulting

Table 2. Compounds **4a–c** Prepared

Substrate	Product	A	Yield[a] (%)	m.p.[b] (°C)	Molecular Formula[c]	IR (KBr)[d] ν (cm^{-1})	MS[e] m/e (%)
2b	**4a**	$-OCH_2-$	89	190–192	$C_{16}H_{19}NO_6$ (321.3)	3000, 1680	221 (78), 206 (100)
2a	**4b**	$-CH_2C(CH_3)_2CH_2-$	96	225	$C_{19}H_{25}NO_4$ (331.4)	2800	331 (85), 191 (100)
2d	**4c**	$-CH_2CH_2CH_2-$	77	190	$C_{15}H_{17}NO_2$ (243.3)	3000	243 (3), 131 (100)

[a] Yield of isolated purified product.
[b] Uncorrected; recorded on a Thomas-Hoover capillary apparatus.
[c] Satisfactory microanalyses obtained: C ±0.32, H ±0.30, N ±0.29.
[d] Recorded on a Perkin-Elmer 137 spectrophotometer.
[e] Recorded on a Perkin-Elmer 270B spectrometer.

oily product is cooled to 25 °C and partitioned between dichloromethane (50 ml) and saturated sodium hydrogen carbonate solution (25 ml). The organic layer is separated, dried with sodium sulfate and concentrated *in vacuo*. The crude products are chromatographed on silica gel (ethyl acetate). Oily products are not subjected to further purification. Solid products are recrystallized from hexane ethyl acetate. In the case of nitro ester **1m** (entry 13, Table 1), the dark red, solid crude product is directly recrystallized from ethanol to afford an analytically pure red powder (Table 1).

Preparation of 4a–c by Addition of 1,3-Dicarbonyl Compounds to 3,4-Dihydroisoquinolines; General Procedure:

The 3,4-dihydroisoquinoline (8.0 mmol) and the corresponding 1,3-dicarbonyl (8.0 mmol) are mixed well at 25 °C and then inserted into an oil bath preheated to 90 °C. Manual stirring is maintained for 30 min and the solid, powdery product is recrystallized from aqueous methanol (Table 2).

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(1) Battersby, A.R., Bink, R., Edwards, T.P. *J. Chem. Soc.* **1960**, 3474.
(2) Gensler, W.J., Bluhm, A.L. *J. Org. Chem.* **1956**, *21*, 336.
(3) Meyers, A.I., Manoz, G.G., Sobotka, W., Barburao, K. *Tetrahedron Lett.* **1965**, 255.
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(11) Yamazaki, T. *Heterocycles* **1978**, *9*, 1717.
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(13) Spath, E., Polgar, N. *Monatsh. Chem.* **1961**, *51*, 190.
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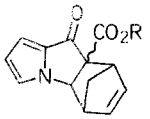
(16) Bobbit, J., Kiely, J., Khanna, K., Ebermann, R. *J. Org. Chem.* **1965**, *30*, 2247.
(17) For another example of this type of reaction see: von Strandtmann, M., Cohen, M.P., Shavel, J. *J. Org. Chem.* **1966**, *31*, 797.
(18) Suendson, A., Boll, P.M. *Tetrahedron* **1973**, *29*, 4251.
(19) Sakane, K., Terayama, K., Haruki, E., Otsuji, Y., Imoto, E. *Nippon Kagaku Kaishi* **1974**, 1535; C. A. **1964**, *81*, 120392.

Errata and Addenda 1987

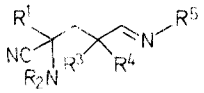
Hall, G., Sugden, J. K., Waghela, M. B.
Page 10. Line 3 of the Abstract should read: dropyrolizines ...
Page 14. The first word of Section 3.11. should be: Benzo[*b*]pyrrolizines.
Page 15. Formula **27** should be:



27

Page 15. The product referred to in Section 4.6., lines 4–5, should be: 10*H*-pyrrolizino[1,2-*b*]quinoline
Page 17. In Section 7., line 4 of the second paragraph should read: **34**.[182] ...

Ahlbrecht, H., von Daacke, A.
Page 24. Formula **8** should be:



8

Costisella, B., Keitel, I.
Page 45. In the heading of the experimental procedure, **6** should read **3** and **8** should read **7**.

Stoss, P., Merrath, P., Schlüter, G.
Page 174. Numbers 1 and 3 should be exhanged in formula **2a–f**.

Singh, G., Deb, B., Ila, H., Junjappa, H.
Page 286. Compounds **1** are 2-aroyl-2-arylthioketene dithioacetals.

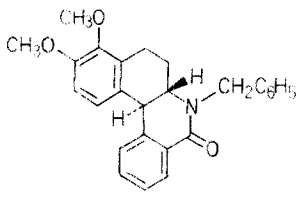
Asaad, F. M., Becher, J., Møller, J., Varma, K. S.
Page 301. Under the reaction scheme, the X group in compounds **3b,d** and **4b,d** should be $CO_2C_2H_5$.

Legrel, P., Baudy-Floc'h, M., Robert, A.
Page 306. The title should read: A One-Pot Synthesis of α-Halohydrazides from 2,2-Dicyanooxiranes.
Page 306. In the table under the reaction scheme, the second heading R^1 should be R^2.

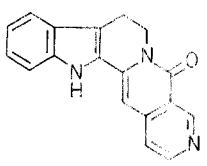
van der Goorbergh, J. A. M., van der Steeg, M., van der Gen, A.
Pages 314–317. The systematic names for the heterocycles involved are: 4,5-dioxo-3,4-dihydro-2*H*,5*H*-thiopyrano[3,2-*c*][1]benzopyrans **4** (RF 24756), 4,5-dioxo-2*H*,5*H*-thiopyrano[3,2-*c*][1]benzopyrans **7** (RF 24756), and 4,5-dioxo-1,3,4,4a,5,10b-hexahydro-2*H*-[1]benzopyrano[4,3-*b*]pyridines **8** (RF 24539).

Attanasi, O. A., Filippone, P., Santensanio, S., Serra-Zanetti, F.
Page 382. In the table under the reaction scheme, R^3 for **1b** should be $CO_2C_2H_5$ and R^3 for **1c** should be CO_2CH_3.

Campbell, A. L., Lenz, G. R.
Pages 428 and 446. Formulae **95** and **298** should be:



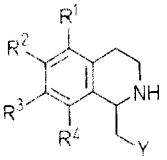
95



298

Page 437. The heading for Table 3 should be: Intermolecular ...

Pelletier, J. C., Cava, M. P.
Page 476. Formula **1a–m** should be:



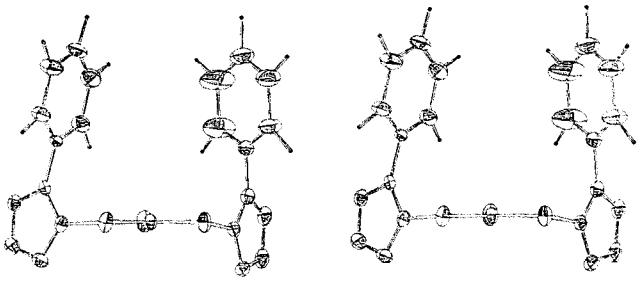
1a-m

L'abbé, G.
Page 528. Compound **45** should be named: 3-(2-pyridyl)-2,4-dithioxo-3,4-dihydro-2*H*-pyrido[1,2-*a*][1,3,5]triazine (RF 9177).

Evans, R. D., Schauble, J. H.
Page 551. Compounds **10** and **11** are tricyclo[2.2.1.0^{2,6}]heptane derivatives.

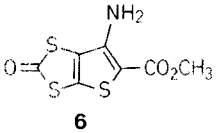
Takeda, K., Tsuboyama, K., Hoshino, M., Kishino, M., Ogura, H.
Page 559. The Y-group for **2g** and **2j** should be furfuryloxy.

Takeda, K., Tsuboyama, K., Takayanagi, H., Ogura, H.
Page 560. The following figure should appear after the 4th paragraph:



Eicher, T., Stapperfenne, U.
Page 625. Compounds **13a,b** are 6,7-dihydrofuro[2,3-*b*]pyridines (RF 7431), and compounds **15a,b** are 1,4-dihydrocyclopentimidazoles (RF 5892).

Dölling, W., Augustin, M., Ihrke, R.
Page 655. Formula **6** should be:



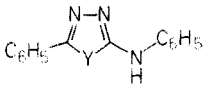
6

Mikołajczyk, M., Bałczewski, P.
Page 661. The second paragraph of ref. 21 should be ref. 22; refs. 22 and 23 should be 23 and 24, respectively.

Rösch, W., Regitz, M.
Page 692. Compounds **21a,b** are 2*H*-1,2,3-diazaphospholes.

Tietze, L.-F., Brumby, T., Pretor, M.
Page 702. Compounds **8** and **9** are 4a,10b-dihydro-4*H*,5*H*-pyrano[3,4-*c*][1]benzopyran-2-carboxylic esters.

Wamhoff, H., Zahran, M.
Page 877. Formula **18a,b** should be:



18a,b

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Page 1039. The target compounds **3** are 1-bromoalkyl aryl ketones.